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American Heart Journal

VOL. 52 DECEMBER, 1956 No. 6

Editorial

POSSIBLE NEW MECHANISMS OF TISSUE DAMAGE IN THE EXPERIMENTAL CARDIOVASCULAR EFFECTS OF ENDOTOXIN

THE view that things similar to the same thing are equal to each other has led to remarkable pitfalls in the biologic sciences, and especially in experimental pathology, where resemblances between the lesions of human disease and pathologic changes occurring during induced abnormal states in animals have sometimes, too early and too easily, been interpreted to mean identity of underlying mechanisms.

With this cautionary preamble, it seems fair to suggest that the endotoxins of gram-negative bacteria[1] may prove to be handy and manageable tools for the study of several unique disturbances of structure and function in the cardiovascular system. This is not to suggest that there are any new revelations concerning the role of endotoxins themselves in human disease; indeed, the lack of such evidence is a reason for the long failure of these materials to attract popular interest in clinical circles. Rather, the current value of endotoxins as tools for research is that they permit close scrutiny, under satisfactory laboratory conditions, of certain new mechanisms by which vascular tissues may undergo damage. Whether these mechanisms bear any basic resemblance to the spontaneous events of human disease remains for future investigation, but new approaches which may lead in this direction seem to have become open.

Among the reproducible pathologic effects of endotoxins in experimental animals are the following: fibrinoid infiltration of the walls of coronary and pulmonary arteries, sometimes but not always associated with frank necrosis of the vessel walls; fibrinoid vegetations implanted on the surface or within the substance of the mitral and aortic valves; occlusion by fibrinoid of the glomerular capillaries, resulting in bilateral cortical necrosis of the kidneys; and similar thrombosis of the sinusoids in the liver and spleen, leading to necrosis in these organs.[2-4] Very extensive degrees of myofiber destruction occur throughout the myocardium, chiefly in the right side of the heart and septum.

The physiologic alterations produced by endotoxins are of equal interest and implication, resembling, on the one hand, the effects of overwhelming intoxication by epinephrine and, on the other, the syndrome of traumatic shock.[1]

From the physiologist's point of view, the endotoxins constitute a vast, remarkably homogeneous class of substances whose biologic properties, regardless of the particular gram-negative organism from which they are extracted,

are indistinguishable. They are known by various terms, depending on the field of interest in which they come under study. In small doses, they are called "bacterial pyrogens"; in larger doses they become the "shock-producing," "Shwartzman-active," "tumor-necrotizing," "abortion-producing," or "vascular" toxins. Some are referred to, unjustifiably, by their parent names, as, for example, "dysentery" or "meningococcal" or "brucella" endotoxin, as if to imply some special connection between the parent and the properties of the endotoxin, despite the fact that the actions of all are, at least qualitatively, the same.

Chemically, all of the endotoxins thus far isolated have proved to be remarkably similar macromolecular complexes containing lipid and polysaccharide, usually bound to a polypeptide or protein. According to Westphal,[5] the lipid is the actual toxic component, whereas the nontoxic polysaccharide behaves as a vehicle which keeps the lipid in solution. The lipid is not demonstrably antigenic and may eventually turn out to be the same substance in all endotoxins, although this remains to be established by further chemical studies. Westphal has shown that the lipid may be artificially transferred from its own polysaccharide to other nonspecific carriers such as casein, with retention of toxicity. It is the lipid which enables endotoxin to become fixed to the surface of erythrocytes, a property which has been fruitfully exploited by Neter and his associates for immunologic studies of endotoxins. It is conceivable that something of this sort may happen when endotoxin is injected into animals, and the toxicity of the lipid may be the result of its capacity to attach itself to components of living cells.

To the immunologist, the endotoxins are familiar as the somatic antigens of gram-negative bacteria, and here the important moiety is the polysaccharide. The antigenicity of the polysaccharide may be involved, as Westphal suggests, in the development of tolerance to endotoxins after repeated injections.[1] The resemblance between the pathophysiologic effects of endotoxin and certain reactions of delayed-type, bacterial allergy, such as tuberculin shock, has been emphasized recently by Stetson,[6] and it is possible that toxicity may be a manifestation of a congenital sort of hyperreactivity analogous to hypersensitivity itself. Somewhat against this notion, but by no means ruling it out, is the observation that endotoxins are highly lethal for the 10-day-old chick embryo.[7]

Two mechanisms which now appear to be involved in the cardiovascular effects of endotoxins are: (1) the participation of fibrinogen in the pathogenesis of fibrinoid lesions of blood vessels, and (2) the participation of epinephrine (or norepinephrine) in the production of tissue necrosis and shock.

The fibrinoid vascular lesions occur when two successive injections of sublethal doses of endotoxin are given by vein in rabbits. During a period of several hours after the second injection, massive intravascular precipitation of a homogeneous, eosinophilic material occurs, and the cardiac and renal lesions of the generalized Shwartzman reaction are the result. The available evidence suggests that the origin of the fibrinoid material is fibrinogen, which becomes altered, following injection of endotoxins, in such a way that it is precipitable by heparin in vitro, and by heparin-like polymers of large molecule size in vivo.[8,9] There is reason to believe that acid polysaccharides derived from leukocytes may act as precipitants of fibrinogen in the generalized Shwartzman reaction.[9]

The similarities between these lesions and changes characteristic of the so-called collagen diseases have been remarked upon by several workers.[10,11] Recently, Gitlin has found immunohistochemical evidence favoring the view that fibrinoid in such diseases is related to fibrinogen or fibrin.[12]

The reaction of shock, which is brought about in a variety of animals by a single, overwhelming dose of endotoxin, seems in some way to be related to epinephrine.[1] The events include, initially, a stage of extreme peripheral arteriolar constriction and vasomotion, accompanied by hyperglycemia, hyperlacticacidemia, and depletion of liver glycogen. During this stage the peripheral vessels exhibit tremendously potentiated responses to topically applied epinephrine (or norepinephrine). The second stage resembles the decompensatory phase of traumatic shock; now, the terminal vessels lose their normal tone, become widely dilated and engorged with motionless blood, and totally unresponsive to epinephrine.[13,14] Some of these effects of endotoxin, including the lethal outcome can be prevented by pretreatment with chlorpromazine, dibenzyline, and cortisone.

Similar effects have been observed, in vitro, in the isolated, perfused rabbit ear preparation.[13,14] Small doses of endotoxin cause heightened vascular responses to epinephrine, while larger doses produce first a loss of reactivity and then a state in which the vessels are actually dilated by epinephrine.

The possibility that epinephrine and norepinephrine may become potent agents of necrotizing tissue damage under the influence of endotoxins is indicated by recent studies of the effects of epinephrine in the skin of endotoxin-treated rabbits.[13,15] When endotoxin is given by vein, an intradermal injection of epinephrine (or norepinephrine) at any time in the following four hours leads to extensive areas of hemorrhagic necrosis of the skin. Similar destructive lesions occur when small amounts of endotoxin and epinephrine are combined and injected into the skin. The damage is not due to endotoxin, but to the altered reactivity to epinephrine, which endotoxin invokes.

Thus, two general mechanisms brought into operation by endotoxins may be causally related to the intoxicating actions of these substances. Whether the intravascular precipitation of fibrinogen in the form of fibrinoid and the potentiation and later exhaustion of reactivity to epinephrine are related to each other, or based on a common underlying mechanism, remains to be learned. At the moment, both appear to offer possible leads to further study of the pathogenesis of fibrinoid in necrotizing vascular lesions and the mechanisms concerned in shock in this and other biologic situations.

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LEWIS THOMAS, M.D.

Original Communications

METHOD FOR THE DETERMINATION OF POTENCY AND WORK OF THE RIGHT VENTRICLE IN PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM: RIGHT VENTRICULAR STRAIN INDEX. I.

H. J. Bidoggia, M.D., J. Cordero Funes, Ph.D., F. E. Labourt, Ph.D., and E. R. Pietrafesa, M.D.

Buenos Aires, Argentina

THE classical method for determining the work of the right ventricle, taking into account the pulmonary artery mean pressure and the cardiac output, can only provide average values. With this method, therefore, it is impossible to assess the potency of the ventricle since it is, by definition, an instantaneous function.

In pulmonary stenosis with an intact ventricular septum, the real average work of the right ventricle will be given by the amount of work which is necessary to overcome the pulmonary stenosis plus the work done by that ventricle to maintain the hemodynamic conditions of the pulmonary system. The above-mentioned classical method can only determine the latter, but provides no indication regarding the ventricular work to overcome the stenosis.

The purpose of this paper is to consider a mathematical method which can enable us to assess the potency and the work done by the right ventricle to overcome the pulmonary stenosis.

After having determined by our method the work of the right ventricle to overcome the stenosis, and the work of the same ventricle to maintain the hemodynamic conditions of the pulmonary system by the classical procedure, we got, with the sum of both data, the total work value.

When the relationship between the total and useful work of the right ventricle was determined, an index which we called the right ventricular strain index was established.

From the Instituto Regional de Cardiología Public Health Department, Carlos Pellegrini, 1432.

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METHOD

According to Starling[1] the work performed by each ventricle during the cardiac systole is totally spent (a) to overcome the resisting pressure in the arterial system and (b) to impress speed to the blood,

$$W = Q \cdot R + \frac{\omega \cdot V^2}{2g} \tag{1}$$

where W = work beat, Q = systolic stroke volume, R = resisting pressure, ω = blood weight, V = blood speed, and g = gravity acceleration.

As the second term of the formula is about 4 per cent of the total in the resting patient, its variations do not affect the estimation of the work performed by the right ventricle.

Therefore, formula (1) is reduced to (1a)

$$W \cong Q \cdot R \tag{1a}$$

The potency ψ of the ventricles is the derivate of the work regarding time (t) in each instant of the systole, that is to say, the quotient limit between the increased work and the time it takes to be increased, when the time variation tends to zero.

$$\psi = \lim_{\Delta t \to 0} \frac{\Delta w}{\Delta t} = \frac{dw}{dt} \tag{2}$$

The ventricular blood flow (F) is the derivative of the volume expelled (q) with reference to time, that is to say, the quotient limit between the diminution of the ventricle volume and the time it takes to diminish that volume when the time tends to zero,

that is

$$F = \lim_{\Delta t \to 0} \frac{\Delta q}{\Delta t} = \frac{dq}{dt} \tag{3}$$

therefore

$$\psi = \frac{dw}{dt} \cong q \frac{dR}{dt} + R \frac{dq}{dt}$$

as when

$\Delta t \to 0$ also $q \to 0$ the first term is annuled,

thus

$$\psi \cong R \frac{dq}{dt} = R \cdot F \tag{4}$$

where ψ = potency, R = pressure, and F = flow.

The values of the instantaneous pressures (R) in the right ventricle (P_v) and in the pulmonary artery were obtained by cardiovascular catheterization according to the Cournand and Ranges[2] technique. The differences between $(P_v - P_p) = \Delta P$ are expressed in Fig. 1.

This value Δ P expresses the instantaneous pressure (R) to be applied in formula (4).

To determine the flow curve (F) in cases of pulmonary stenosis we applied the Bernouilli[3] laws ruling the way out of the fluids through the small orifices, since the relationship between the minimum diameter of the ventricle and the maximum one of the valve fulfill the conditions established in his laws.

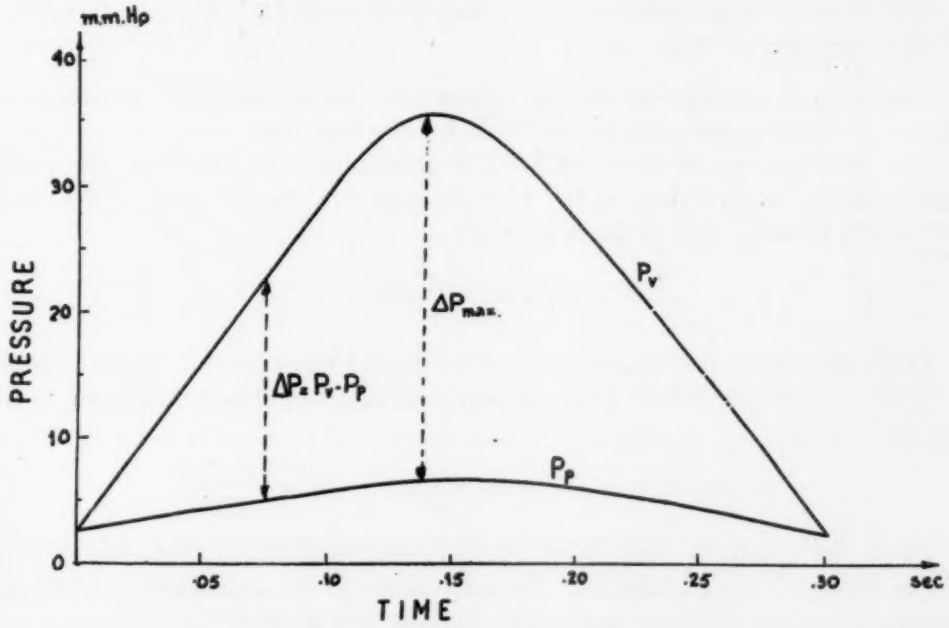

Fig. 1.—Relationship of ΔP (right ventricular systolic pressure P_v minus pulmonary artery systolic pressure P_p) to time.

Therefore, in these cases, the flow is directly proportional to the square root of the difference of instantaneous pressures on both sides of the stenosis, that is to say

$$F = K \sqrt{P_v - P_p} \qquad (5)$$

where F = flow,
K = constant depending on the unities, the characteristics of the system, and the qualities of the fluid,
P_v = instantaneous pressure in the right ventricle, and
P_p = instantaneous pressure in the pulmonary artery.

To apply formula (5) to find out the flow curve we have to know the constant K. Being impossible to determine its value since we do not know the characteristics of the system we shall arbitrarily suppose K = 1.

In Fig. 1 we divide the systolic period into a proper number of equal parts; the ordinates in each of these instants provide the ventricular (P_v) and the pulmonary pressures (P_P). Carrying these values to formula (5), where, according to our convention K = 1, we get the corresponding values of F for each point; joining them we have the flow curve (Fig. 2) on an arbitrary scale, since in fact K = 1.

We will develop the following procedure to calculate the flow scale. First we determine the average ordinate of the flow curve (Fig. 2) according to Simpson's[4] rule.

$$M.V. = \frac{\frac{F_o}{2} + F_1 + F_2 + \ldots\ldots F_{n-1} + \frac{F_n}{2}}{n} = \frac{1}{n}\left[\frac{F_o + F_n}{2} + \sum_{i=1}^{i=n-1} F_i\right] \qquad (6)$$

where M.V. = average ordinate, Fi = flow in the point i, being i = 0, 1, 2...n, and n = numbers of intervals.

The average ordinate of the flow curve can also be obtained by planimetric integration dividing the area of the curve by the base line.

The average systolic flow (M.S.F.) is determined by dividing the cardiac output, estimated according to the Fick principle[5] by the product of the cardiac rate (r) and the duration of the systole (t).

$$M.S.F. = \frac{C.O.}{r \cdot t} \qquad (7)$$

If in the chosen flow curve (Fig. 2) K should have its real value instead of the arbitrary one, the value of the average ordinate would be the systolic average flow; then

$$K \text{ (real)} \times M.V. = M.S.F. \quad \therefore \quad K = \frac{M.S.F.}{M.V.} \qquad (8)$$

As in the arbitrary flow curve K was considered equal to 1, the real flow scale is obtained by multiplying the real value of K calculated according to formula (8) by the arbitrary scale (Fig. 2, right side scale).

According to formula (2) the potency is obtained by multiplying the corresponding ordinates of the curve of pressure difference in the right ventricle and in the pulmonary artery ($P_v - P_p$) (Fig. 1) by those of flow (Fig. 2). With these values the potency curve necessary to overcome the stenosis during the expelling period is obtained (Fig. 3), the maximum ordinate being the maximum potency (ψ mx). The area of this potency curve represents the work done by the right ventricle to overcome the stenosis during the systolic period (W_s S).

The work done by the right ventricle within a minute to overcome the pulmonary stenosis (W_s) is obtained by multiplying the systolic work (W_s S) by the cardiac rate (r) and is expressed in kilogram-meters.

$$W_s = W_s S \times r \qquad (9)$$

The work of the right ventricle to maintain the normal hemodynamic condition through the pulmonary circuit, that is to say, the right ventricular useful work, is given by multiplying the cardiac output by the mean pulmonary artery pressure.

$$Wu = C.O. \times P_p \ (md) \qquad (10)$$

The sum of both works obtained (Wt), expresses the total work done by the right ventricle.

$$Wt = Ws + Wu \qquad (11)$$

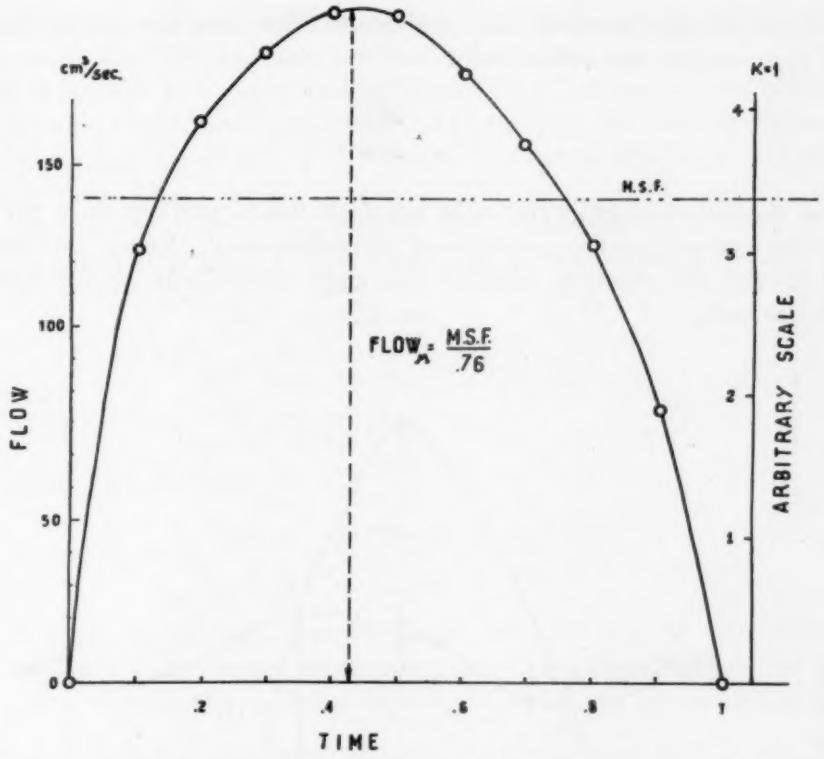

Fig. 2.—Relationship of pulmonary flow to time. Systolic flow curve according to the formula: Flow = $K\sqrt{P_v - P_p}$ where P_v = instantaneous right ventricular systolic pressures, P_p = instantaneous pulmonary artery pressures, and $K = 1$ (right scale). In this chosen case the mean systolic flow $M.S.F. = \frac{\text{cardiac output}}{\text{heart rate} \times \text{systolic period}} = 140$ c.c. per second. The systolic flow was calculated for every 1/10 of the total systolic period (small circles).

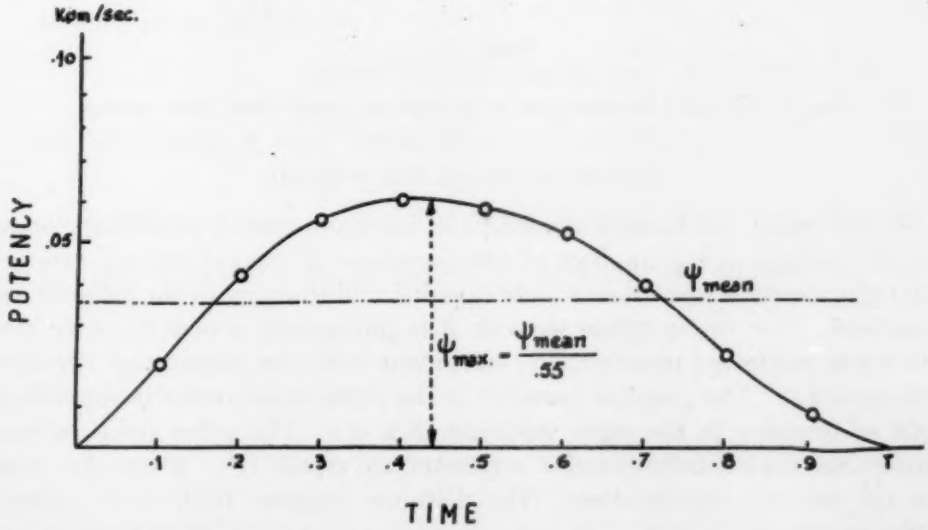

Fig. 3.—Relationship of right ventricular potency (ψ) to time. This curve was built according to the formula: potency = $R \times F$ where R = instantaneous systolic pressure differences between the right ventricle and the pulmonary artery, and F = instantaneous systolic flow.

The relationship between the total work (Wt) and the useful work (Wu) is called right ventricular strain index.

$$I = \frac{Wt}{Wu} \tag{12}$$

As in normal conditions the right ventricle has to perform only the work to pressure the hemodynamic condition of the pulmonary system, the total work is equal to the useful work; thereby the right ventricular strain index being equal to the unity.

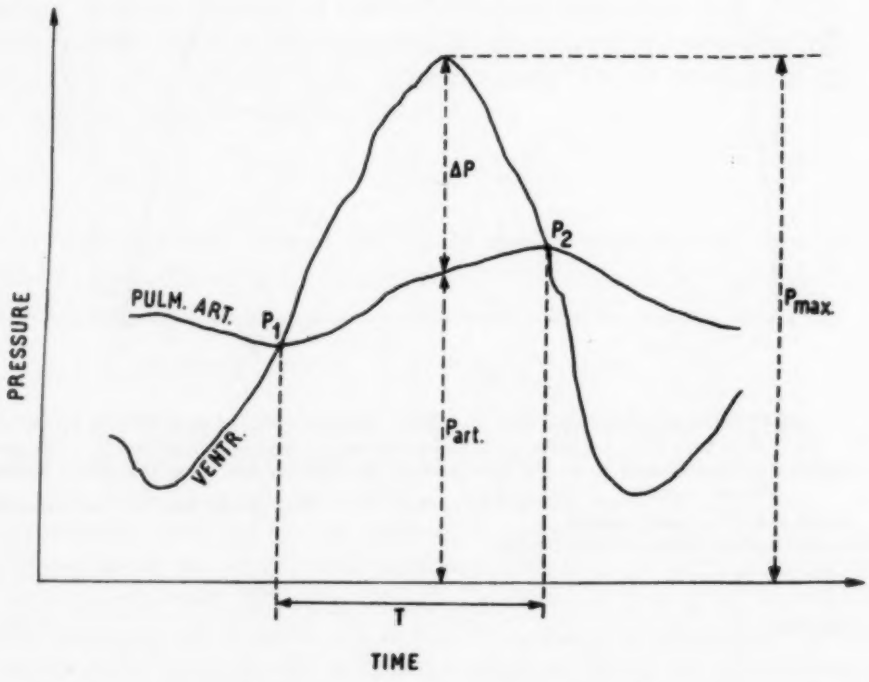

Fig. 4.—Graphical determination of the systolic period of the right ventricle.

PRACTICAL USE OF THE METHOD

We will apply the foregoing method to a specific case of pulmonary stenosis. Once the corresponding tracings of the pressures in the pulmonary artery and in the right ventricle are obtained, the opening and shutting of the sigmoid valves are marked. For this purpose we seek in a pulmonary artery pressure tracing the point of minimum pressure (Pi) coincident with the moment of the sigmoid valves opening. The pressure complex in the pulmonary artery is superimposed on one of pressure in the right ventricle (Fig. 4). The other point where the pressures on both cardiovascular segments are equal (P_F) gives the moment when the sigmoid valves close. The distance between both marks gives the systolic period (T).

On a pair of Cartesian orthogonal coordinate axes, the pressure and time scales are traced (Fig. 1), making the zero of the time scale coincident with the

opening of the sigmoid valves. In this system, eleven values of the ventricular and pulmonary systolic pressures are marked at equal intervals.

To find out the flow curve we apply formula (5) on each of the eleven points of the pressure curve making arbitrarily K = 1, so that eleven values of the instantaneous flow are obtained. These values are carried to a new system of coordinates (Fig. 2).

To get the real scale we determine the average ordinate (M.V.) and the average systolic flow (M.S.F.), thus obtaining the real value of K.

$$M.V. = 3.38 \text{ cm.}, \tag{6}$$

$$M.S.F. = 139 \text{ cm.}^3 \text{ per second, and} \tag{7}$$

$$K = 41.1 \ . \tag{8}$$

Therefore, the real scale is:

$$\frac{139 \text{ cm.}^3/\text{sec.}}{3.38 \text{ cm.}} = \frac{41.1 \text{ cm.}^3/\text{sec.}}{\text{cm.}}$$

By multiplying the difference of pressures by the flow in each of the eleven points considered in the curves, eleven points are obtained with which we build the potency curve of the right ventricle in order to overcome the pulmonary stenosis (Fig. 3).

$$\psi = (P_v - P_p) \cdot F. \frac{13.6 \times 1.055}{1.000} \tag{4}$$

1.055 being the specific blood weight and 13.6 being the specific mercury weight, factors of conversion necessary to obtain the potency in kilograms per second if the pressures are expressed in millimeters of mercury and the volumes in liters per second.

The maximum potency is:

$$\psi \text{ mx.} = 0.073 \text{ Kg.-m./sec.}$$

The right ventricle work during the systolic period to overcome the stenosis is:

$$W_v S = 0.0103 \text{ Kg.-m.}$$

The right ventricle work per minute to overcome the stenosis is:

$$W_v = 0.0103 \times 87 = 0.90 \text{ Kg.-m.} \tag{9}$$

The useful work is:

$$Wu = 8 \times 3.51 \times \frac{13.6 \times 1.055}{1.000} = 0.41 \text{ Kg.-m./min.} \tag{10}$$

The total work is:

$$Wt = 0.90 + 0.41 = 1.31 \text{ Kg./min.} \tag{11}$$

The right ventricular strain index is:

$$I = \frac{1.31}{0.41} = 3.2 \qquad (12)$$

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TABLES FOR CALCULATING THE POTENCY AND WORK OF THE RIGHT VENTRICLE AND THE RIGHT VENTRICULAR STRAIN INDEX IN PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM. II

J. Cordero Funes, Ph.D., F. E. Labourt, Ph.D., E. R. Pietrafesa, M.D., and H. J. Bidoggia, M.D.

Buenos Aires, Argentina

THE method to calculate the potency and the work of the right ventricle and the right ventricular strain index in cases of pulmonary stenosis with intact ventricular septum, worked out in the previous paper,[1] is very accurate inasmuch as it adapts itself to the minor parametric variations. Nevertheless, this is not easy to handle due to it requiring hard mathematical work.

Repeated application of the method to specific cases led us to deduce certain fundamental relations, which, conveniently combined, allow us to reduce the mathematical work, making it almost insignificant.

In order to clarify the theoretical basis which led us to the above-mentioned simplification, one must consider successively the six essential aspects of its development.

A. *Shape of the Curve of the Difference of Pressures Between the Right Ventricle and the Pulmonary Artery.*—The most important part of the right ventricle and pulmonary artery tracings from the point of view of pulmonary stenosis is that which corresponds to the systolic period. It is in that moment when the difference of pressures between the right ventricle and the pulmonary artery, which is the cause of the right ventricular strain, is clearly seen. Since it was shown[1] that the conditions of the Bernouilli's theorem[2] are fulfilled in pulmonary stenosis, it was a fair assumption that the shape of the curves of the pressure difference in every patient must be very similar to each other, especially in those cases with marked stenosis. In a tracing five times photographically enlarged to enable its detailed study, the systolic period T was marked according to the technique already given in Paper I. It was divided into ten equal parts and at each point the differences of pressure were measured between the right ventricle (P_v) and the pulmonary artery (P_p). To do that, it was necessary to superimpose the pressure tracings of the right ventricle and the pulmonary artery in such a way that the times of valvular opening and shutting coincided. The same procedure was applied to several complexes of the tracing, and afterward the average values

From the Instituto Regional de Cardiología, Public Health Department, Carlos Pellegrini, 1432.

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of the homologous points* were established, thus obtaining the pressure differences at each one of those homologous points (first row of Table I). These values were expressed in percentages, making the value of the maximum pressure difference equal to 100 (5T of Table I).

$$\Delta P = \frac{P_v - P_p}{(P_v - P_p)\ Mx.} \times 100$$

Thus one obtained P_o for T = 0; P_1 for T/10; P_2 for 2T/10; and so on, which may be seen in Table I, second row.

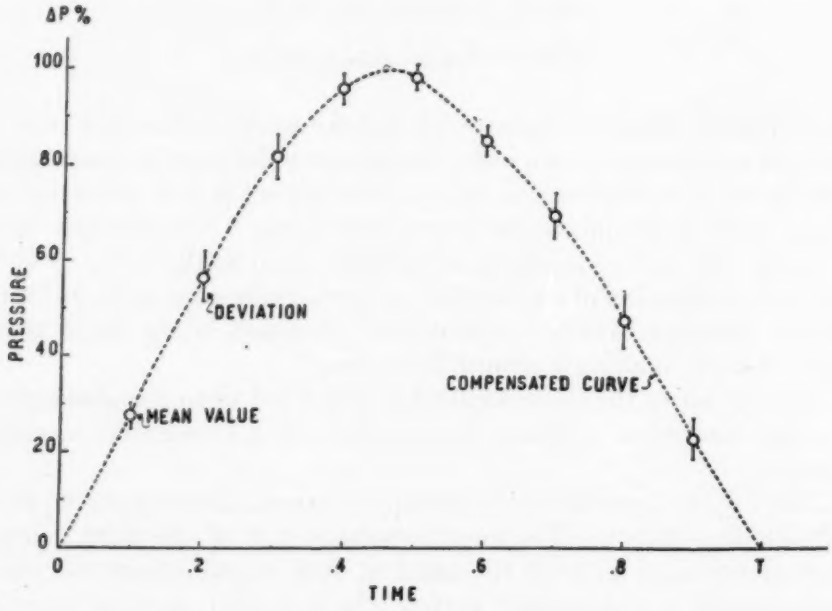

Fig. 1.—Graphical representation of the statistical study of Table II.

Repeating this procedure for all patients, we obtained for each homologous point very similar percentages. The statistical study appears in Table II. The second row indicates the averages and the third the standard error of the average for each point. Both rows of Table II are graphically represented in Fig. 1 where the observed averages are shown with a circle, the standard deviation from the average with a vertical bar, and the compensated curve, which fits the experimental data best, with a dotted line.

The smallness of the individual variations (the standard error of the average is never more than 8 per cent) confirms the hypothesis that the shape of the curve of the difference of pressures between the right ventricle and the pulmonary artery is the same in every case.

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*The homologous points are those which always correspond to the same fraction of the systolic period T, that is to say T/10; 2T/10; 3T/10; 4T/10; and whatever the real duration of period T may be.

TABLE I. RELATIONSHIP OF ΔP [VENTRICLE PRESSURE (P_V) MINUS PULMONARY PRESSURE (P_P)] TO SYSTOLIC PERIOD (T)

T / ΔP	.1T	.2T	.3T	.4T	.5T	.6T	.7T	.8T	.9T	T
$P_V - P_P$	10.6	19.3	21.4	37.4	40.5	38.0	30.0	20.0	11.4	0
ΔP in %	26	48	72	92	100	93	74	49	28	0

B. *Relationship During the Systolic Period Between Δ P Mx. (Greatest Difference of Pressure Between the Right Ventricle and the Pulmonary Artery) and Δ P Md. (Average of the Pressure Differences Between These Two Segments).*—As a consequence of the previous result it becomes evident there is constant relationship between Δ P Mx. and Δ P Md. in all cases. This constant is called "a" and its value is:

$$a = \frac{\Delta P\ Md.}{\Delta P\ Mx.} = \frac{1/T \int_o^T f(t)\ dt^*}{(P_v - P_p)\ Mx.}$$

where f (t) = Δ P instantaneously (Fig. 1). This function is easily expressed in a power series and can be integrated within the interval 0→T. Having carried out these operations the result was:

$$a = 0.60$$

C. *Relation Between the Maximum Potency and the Average Potency of the Right Ventricle to Overcome Stenosis.*—According to the Bernouilli's laws, the flow is proportional to the square root of the difference of pressures on each side of the stenosis.

$$F = K \sqrt{\Delta P}$$

As the potency is $\psi = \Delta P \cdot F$

$$\text{so } \psi = \Delta P \cdot K \cdot \sqrt{\Delta P} = K \cdot \Delta P^{3/2}$$

TABLE II. STATISTICAL STUDY IN 15 PATIENTS

T / ΔP	.1T	.2T	.3T	.4T	.5T	.6T	.7T	.8T	.9T	T
ΔP average	28.5	57.5	81.5	95.0	97.5	86.5	70.0	49.0	23.0	0
S-T deviation	1.4	4.5	3.7	1.6	0.7	2.4	3.1	3.3	2.0	0

*The integral is the mathematical definition of the average values.

As the curve representative of pulmonary artery pressure for all cases of stenosis has the same shape it follows that the ratio between the maximum and the average potency is a constant, thus

$$b = \frac{\psi \text{ average}}{\psi\ Mx.} = \frac{1/T \int_o^T \psi\, dt}{\psi\ Mx.}$$

Substituting

$$b = \frac{1/T \int_o^T K.\ \Delta\ P^{3/2}\, dt}{K.\ \Delta\ P_{Mx.}^{3/2}} = \frac{1}{T}\ \frac{\int_o^T \Delta\ P^{3/2}\, dt}{\Delta\ P_{Mx.}^{3/2}}$$

As can be seen, the constant K, which is different for each case, has disappeared in the quotient, a fact which is in accord with the previous hypothesis. Developing $\Delta\ P = f\ (t)$ as before and integrating it, the result obtained was

$$b = 0.51$$

D. *The Maximum Potency of the Right Ventricle to Overcome Stenosis.*— As was seen:

$$\psi\ Mx. = \Delta\ P\ Mx. \times \frac{13.6 \times 1.005}{1.000}$$

where the numerical term serves for the conversion of the units. The maximum difference of pressures between the right ventricle and the pulmonary artery is read from the tracing; on the other hand the flow at the same instant (also a maximum) can be calculated by the following procedure by Bernouilli:

$$F_{Mx.} = K.\ \sqrt{\Delta\ P_{Mx.}} = K.\ \Delta\ P_{Mx.}^{1/2}$$

To be able to calculate the constant K, which is the unknown quantity peculiar to each patient, one uses the values which are given by the hemodynamic study.

Mean systolic flow = $M.S.F. = K.\ \sqrt{\Delta\ P}\ Md.$

then

$$K = \frac{M.S.F.}{\Delta\ P_{Md.}^{\frac{1}{2}}}$$

since $\Delta\ P\ Md. = 0.6\ \Delta\ P_{Mx.}$ according to A.

Therefore

$$K = \frac{M.S.F.}{\Delta\ P_{Md.}^{\frac{1}{2}}\ \sqrt{0.6}}$$

Substituting

$$F_{Mx.} = \frac{M.S.F.}{\Delta\ P_{Mx.}^{\frac{1}{2}}\ \sqrt{0.6}}\ \Delta\ P_{Mx.}^{\frac{1}{2}} = \frac{M.S.F.}{0.77}$$

Therefore the maximal potency is:

$$\psi\, Mx. = \Delta\, P_{Mx.} \cdot \frac{M.S.F.}{0.77} \cdot \frac{13.6 \times 1.055}{1.000}$$

as

$$M.S.F. = \frac{C.O.}{r \cdot T}$$

it results

$$\psi_{Mx.} = \Delta\, P_{Mx.} \cdot \frac{C.O.}{r \cdot T} \times 0.0186 \qquad (1)$$

Where the potency is expressed in kilogram-meters per second if pressure is given in mm. Hg, the cardiac output in liters per minute, cardiac rate in beats per minute, and the systolic period in seconds.

E. *Work of the Right Ventricle in Overcoming Stenosis.*—The systolic work done by the right ventricle in overcoming stenosis (W_S) is the integral potency (instantaneous) applied to the whole ejection period; as a consequence

$$W_s = \int_0^T \psi\, dt$$

using the average potency

$$\psi_{average} = \frac{1}{T} \int_0^T \psi\, dt$$

therefore

$$W_s = \psi_{average} \cdot T$$

remembering the relation of C. among the average, systolic, and maximum potency, one gets

$$\psi_{average} = b\psi_{Mx.}$$

therefore

$$W_s = 0.51 \times T \times \psi_{Mx.}$$

and per minute the work done by the right ventricle in overcoming the stenosis W_s is

$$W_s = 0.51 \times T \times r \times \psi_{Mx.}$$

replacing $\psi_{Mx.}$ according to formula (1),

$$W_s = \Delta\, P_{Mx.} \times C.O. \times 0.0095 \qquad (2)$$

F. *Right Ventricle Strain Index.*—By definition the strain index is

$$S.I. = \frac{W.\ \text{total}}{W.\ \text{useful}} = \frac{Wu + Ws}{Wu}$$

The useful work can be calculated by the classical formula

$$Wu = C.O. \times P.A._{Md.} \times \frac{13.6 \times 1.005}{1.000}$$

where $P.A._{Md.}$ = Pulmonary artery mean pressure and the work done to overcome the stenosis by formula (2)

$$W_s = \Delta P_{Mx.} \times C.O. \times 0.0095$$

therefore

$$S.I. = \frac{C.O. \ (\Delta P_{Mx.} \times 0.0095 + P.A._{Md.} \times 0.00143}{C.O. \times P.A._{Md.} \times 0.00143}$$

$$S.I. = 1 + \frac{\Delta P_{Mx.}}{P.A._{Md.}} \ 0.66 \qquad (3)$$

TABLE III. RIGHT VENTRICULAR WORK PER MINUTE TO OVERCOME THE PULMONARY STENOSIS

ΔP \ C.O.	2	3	4	5	6	7	8	9	10	11	12
190	3.61	5.41	7.22	9.01	10.82	12.64	14.44	16.23	18.02	19.90	21.64
170	3.23	4.85	6.46	8.08	9.70	11.30	12.92	14.54	16.16	17.75	19.40
150	2.85	4.28	5.70	7.12	8.56	10.00	11.40	12.84	14.24	15.70	17.12
140	2.67	3.99	5.34	6.65	7.98	9.31	10.68	11.97	13.30	14.63	15.96
130	2.47	3.71	4.94	6.18	7.42	8.64	9.88	11.13	12.36	13.57	14.84
120	2.28	3.42	4.56	5.70	6.84	7.98	9.12	10.26	11.40	12.52	13.68
110	2.09	3.13	4.18	5.22	6.26	7.31	8.36	9.39	10.44	11.50	12.52
100	1.90	2.85	3.75	4.75	5.70	6.65	7.60	8.55	9.50	10.30	11.40
90	1.71	2.57	3.42	4.27	5.13	6.00	6.84	7.70	8.55	9.41	10.20
80	1.52	2.28	3.04	3.80	4.56	5.32	6.08	6.84	7.60	8.36	9.10
70	1.33	2.00	2.67	3.33	4.00	4.67	5.33	6.00	6.66	7.32	8.00
60	1.14	1.70	2.28	2.85	3.43	4.00	4.57	5.15	5.70	6.28	6.85
50	0.95	1.43	1.90	2.38	2.85	3.33	3.80	4.28	4.76	5.23	5.71
40	0.76	1.14	1.52	1.90	2.28	2.67	3.04	3.42	3.70	4.17	4.56
30	0.57	0.85	1.14	1.43	1.70	2.00	2.28	2.57	2.85	3.13	3.42
20	0.38	0.57	0.76	0.95	1.14	1.33	1.51	1.70	1.89	2.08	2.26
15	0.28	0.42	0.57	0.71	0.85	1.00	1.14	1.28	1.42	1.56	1.71
10	0.19	0.28	0.38	0.47	0.57	0.67	0.76	0.85	0.94	1.04	1.13

C.O. = Cardiac output.
Δ P = Greatest difference of pressure during systolic period between the right ventricle and the pulmonary artery.

TABLE IV. RIGHT VENTRICULAR MAXIMUM POTENCY

r . t \ Ws	1	2	3	4	5	6	7	8	9	10
40	.049	.098	.147	.196	.245	.295	.343	.392	.440	.490
35	.056	.112	.168	.223	.280	.335	.391	.447	.590	.560
30	.065	.130	.196	.262	.327	.392	.457	.522	.587	.650
25	.078	.156	.235	.313	.392	.470	.550	.627	.705	.784
20	.098	.196	.294	.392	.490	.590	.685	.785	.880	.980
15	.130	.260	.392	.524	.654	.784	.914	1.04	1.17	1.30

W_s = Right ventricular work to overcome pulmonary stenosis.
r = Cardiac rate.
T = Average duration of the systolic period.

The three equations have been tabulated for greater ease. To calculate the work done by the right ventricle per minute in overcoming the stenosis, one makes use of Table III where the cardiac output C.O. in liters is found in the upper row and the difference of maximal pressure between the right ventricle and the pulmonary artery Δ P, expressed in mm. Hg, is found in the left column. The result is expressed in kilogram-meters per minute.

TABLE V. RIGHT VENTRICULAR STRAIN INDEX

Right Ventricular Maximum Pressure Minus Homologous Pulmonary Artery Pressure	Pulmonary Artery Mean Pressure 8	9	10	11	12	13	14	15	16	17	18
5	1.41	1.37	1.33	1.30	1.27	1.25	1.24	1.22	1.20	1.19	1.18
10	1.83	1.73	1.66	1.60	1.55	1.51	1.47	1.44	1.41	1.39	1.38
15	2.24	2.11	1.99	1.90	1.83	1.77	1.71	1.66	1.62	1.58	1.55
20	2.65	2.47	2.32	2.20	2.10	2.02	1.94	1.88	1.82	1.77	1.73
25	3.07	2.83	2.65	2.50	2.38	2.27	2.18	2.10	2.03	1.97	1.91
30	3.48	3.20	2.98	2.80	2.65	2.52	2.41	2.32	2.24	2.17	2.10
35	3.89	3.57	3.31	3.10	2.93	2.78	2.65	2.54	2.44	2.36	2.28
40	4.30	3.92	3.63	3.39	3.20	3.03	2.88	2.75	2.64	2.55	2.46
45	4.71	4.30	3.96	3.70	3.48	3.29	3.12	2.98	2.85	2.74	2.65
50	5.13	4.67	4.30	4.00	3.75	3.53	3.35	3.20	3.06	2.94	2.83
55	5.54	5.03	4.62	4.29	4.03	3.78	3.59	3.41	3.26	3.14	3.01
60	5.95	5.40	4.95	4.61	4.31	4.06	3.83	3.65	3.42	3.34	3.21
65	6.35	5.76	5.27	4.89	4.57	4.30	4.06	3.85	3.67	3.51	3.38
70	6.77	6.12	5.60	5.17	4.83	4.54	4.28	4.07	3.87	3.70	3.55
80	7.60	6.86	6.27	5.79	5.39	5.06	4.76	4.51	4.29	4.09	3.93
90	8.42	7.61	6.95	6.40	5.94	5.56	5.24	4.95	4.70	4.49	4.30
100	9.25	8.34	7.60	7.00	6.50	6.09	5.71	5.40	5.12	4.88	4.67
110	10.08	9.05	8.25	7.59	7.05	6.57	6.17	5.84	5.52	5.27	5.04
120	10.88	9.81	8.92	8.20	7.60	7.10	6.67	6.28	5.95	5.67	5.40
130	11.72	10.56	9.56	8.82	8.17	7.61	7.13	6.71	6.36	6.05	5.78
140	12.55	11.25	10.22	9.42	8.72	8.12	7.61	7.16	6.78	6.43	6.13
150	13.40	12.05	10.91	10.05	9.26	8.64	8.08	7.63	7.20	6.83	6.52
160	14.20	12.71	11.55	10.60	9.78	9.10	8.52	8.02	7.57	7.20	6.85

To calculate the maximum potency developed by the right ventricle one makes use of Table IV.

In the upper row we have the work done by the right ventricle to overcome the stenosis W_s which has been found in the previous step. In the left column we have the product of the systolic period, expressed in seconds, multiplied by the heart rate (r. t). The result is given in kilogram-meters per second.

To calculate the right ventricular strain index we use Table V (based on formula 3). In the upper row we have the mean pulmonary artery pressure, and in the column to the left we have the difference between the maximum pressures of the right ventricle and the pulmonary artery. The value of the index is a number without any physical significance.

In order to simply the calculus of the maximum potency we leave $\Delta P_{Mx.}$ out of formula (2);

$$\Delta P_{Mx.} = \frac{W_s}{C.O. \times 0.0095}$$

Substituting it in formula (1) we get

$$\psi_{Mx.} = \frac{W_s}{C.O. \times 0.0095} \times \frac{C.O.}{r \cdot t} \quad 0.0186$$

$$\psi_{Mx.} = \frac{W_s}{r \cdot t} \quad 1.96$$

which is the formula we used to build up Table IV, allowing us to leave the cardiac output out of the calculus.

COMMENTARY

The work of the approximations obtained is clearly seen in comparative Table VI. There the values obtained for using the formulas given in Paper I and the values obtained using Tables III, IV, and V have been compared.

TABLE VI. COMPARATIVE VALUES BY ANALYTICAL METHOD AND BY MEANS OF THE TABLES OF RIGHT VENTRICULAR POTENCY, RIGHT VENTRICULAR WORK PER MINUTE TO OVERCOME THE PULMONARY STENOSIS, AND RIGHT VENTRICULAR STRAIN INDEX

NO.	PATIENT	MAX. POTENCY			STENOSIS WORK			R. V. STRAIN INDEX		
		CAL.	TAB.	ERROR	CAL.	TAB.	ERROR	CAL.	TAB.	ERROR
1	D. D.	.274	.246	−10	4.33	3.82	−12	7.2	6.5	− 9.7
2	L. M.	.185	.187	+ 1	3.51	3.20	− 9	6.7	5.9	−11.8
3	J. F.	.344	.347	+ 1	4.82	4.44	− 8	5.2	4.9	− 6.5
4	C. B.	.205	.196	− 4	2.74	2.52	− 8	5.0	4.6	− 8.0
5	P. G.	.496	.452	− 9	4.06	4.40	+ 8	4.2	4.6	+ 9.5
6	E. S.	.131	.125	− 5	2.04	1.90	− 7	4.0	3.7	− 7.5
7	R. M.	.073	.064	−12	.90	.83	− 8	3.2	3.1	− 3.3
8	M. C.	.114	.100	−12	1.27	1.23	− 3	2.8	2.7	− 3.5
9	C. F.	.359	.296	−16	3.78	3.48	− 8	2.2	2.2	0
10	L. O.	.070	.054	−22	.73	.71	− 3	1.9	1.9	0
11	A. C.	.104	.110	+ 6	1.74	1.67	− 4	1.8	1.8	0
12	J. M.	.076	.075	− 1	1.34	1.13	−16	1.7	1.6	− 5.9
13	M. S.	.146	.125	−15	1.53	1.38	−10	1.7	1.7	0
14	N. C.	.050	.047	− 6	.84	.74	−12	1.4	1.3	− 7.0
15	N. B.	.039	.030	−23	.48	.40	−16	1.2	1.2	0

It should be noticed that in no case was the error greater than 11.8 per cent and as a whole, the average error was within 7 per cent, which is good enough for clinical purposes.

In this paper we have tried to replace the complicated mathematical calculus by the use of tables which give an easier way to value: the maximal potency of the right ventricle, the total work per minute of the right ventricle to overcome pulmonary stenosis, and the right ventricular strain index, in cases of pulmonary stenosis.

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RIGHT VENTRICULAR STRAIN INDEX IN PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM: ITS VALUE IN CLINICAL WORK. III

E. R. Pietrafesa, M.D., F. E. Labourt, Ph.D., J. Cordero Funes, Ph.D., and H. J. Bidoggia, M.D.

Buenos Aires, Argentina

THE study of the circulatory physiopathology has advanced considerably of late mainly because of the systematic use of the method of cardiovascular catheterization.

A daily clinical problem in a clinic is the estimation of the role the right heart plays in some congenital cardiovascular malformations. Thus, the clinic allowed us through its classical methods to estimate approximately the modifications and adaptations of the right ventricle as a consequence of some anomalies. However, it is difficult without the modern methods to have an accurate idea of the way and degree in which this congenital malformation disturbs the functioning of the right ventricle.

Several attempts have been made in pulmonary stenosis with an intact ventricular septum to gather useful data for the clinical appraisal of the patient. Thus Gorling and associates[1] were able to calculate the pulmonary valvular area and Silber and colleagues[2] proposed an index which indicates "an approximated numerical expression of the dynamic signification of the pulmonary stenosis."

With the object of finding new data which could evaluate the functional capacity of the right ventricle in cases of pulmonary stenosis we undertook to study the determination of the potency and work of the right ventricle.[3-4] It having been made possible to determine the total work of the right ventricle (Wt), that is to say, the sum of the work it performs to overcome the pulmonary stenosis and that necessary to maintain the hemodynamic conditions of the pulmonary system for useful work (Wu), we established the relationship between them $\left(\frac{Wt}{Wu}\right)$ obtaining a value we call right ventricular strain index (R.V.S.I.).

It is the purpose of this paper to relate the clinical picture of the patients suffering from pulmonary stenosis with the right ventricular strain index.

MATERIAL AND METHODS

This study includes fifteen patients having pulmonary stenosis with an intact ventricular septum. In six of these cases (2, 3, 4, 7, 13, and 15) the coexistence of an interauricular septal defect was demonstrated, it having also been observed

From the Instituto Regional de Cardiología, Public Health Department, Carlos Pellegrini, 1432.

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that in two of them (7 and 13) there was an anomalous pulmonary vein draining into the right auricle. Another case (11) with an anomalous pulmonary vein was also found, in which it had not been possible to demonstrate an interauricular septal defect.

Right heart catheterization was performed according to the Cournand and Ranges[5] technique.

For blood oxygen determinations a Van Slyke-Neill apparatus was used. The oxygen consumption per minute was calculated by making the patient breathe room air for three or four minutes and collecting the expired air in a 100 liter Tissot gasometer. The samples were later analyzed in a Haldane apparatus.

The cardiac output was calculated by applying the Fick principle. In cases of pure pulmonary stenosis blood samples from the femoral and pulmonary arteries were simultaneously taken to calculate the arteriovenous oxygen content difference. In cases with an interauricular septal defect or an anomalous venous return the oxygen difference between the blood samples from the femoral artery and the average oxygen content of both venae cavae was calculated.

The cardiac index was calculated by dividing the cardiac output by the body surface, determined according to the Boothy and Sandiford tables.

The intracardiovascular pressures were obtained with a Hamilton manometer with metalic membranes. In every case, a continuous pressure tracing was taken from the pulmonary artery to the right ventricle. According to the tracings obtained our patients were classified in three types following the pattern provided by Kiklin and associates[6], that is to say, valvular (Cases 2, 3, 6, 8, 9, and 13), infundibular (1, 4, 5, and 10) and combined valvular and infundibular (7, 11, 12, 14, and 15).

The pulmonary valvular area (A) was calculated by the Gorlin and Gorlin[1] formula. The diameter of this valve (D) was given by the formula $D = 1.13\ A$, admitting that the area is nearly circular during the systolic period. The stenosis index, proposed by Silber and associates[2] was also calculated in every case.

In all the observations, the maximum potency, and the useful and total work of the right ventricle to overcome the stenosis, as well as its strain index, were estimated by the method given in Paper I.[3] The maximum potency, the work to overcome the stenosis, and the right ventricular strain index were also calculated according to the tables in Paper II.[4]

RESULTS

Table I shows the physiologic data obtained in this group. In Table II the right ventricular strain index is compared with: (a) the stenosis index proposed by Silber and associates, (b) the pulmonary valvular area, (c) the cardiac index, and (d) the clinical, radiologic, and electrocardiographic findings.

In Cases 1 through 6, the cardiac index was low, the pulmonary valvular area was small, and the right ventricular strain index was well above those of the other observations. All but Case 5 showed signs of cardiac insufficiency. The stenosis index of Silber and associates also proved to be higher in these six observations than in the others, but the differences among them were remarkable.

TABLE I. PHYSIOLOGIC STUDIES IN PULMONIC STENOSIS

CASE	NAME	TYPE OF PULMONIC STENOSIS AND ASSOCIATED MALFORMATIONS	HEART RATE PER MINUTE	BODY SURFACE M.²	O_2 CONSUMPTION (C.C./MIN.)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX $\left(\frac{\text{L.}}{\text{M.}^2/\text{MIN.}}\right)$	RIGHT VENTRICULAR MAXIMUM PRESSURE (MM. HG)	PULMONARY SYSTOLIC PRESSURE (MM. HG)	PULMONARY MEAN PRESSURE (MM. HG)	SILBER ET AL. STENOSIS INDEX $\left(\frac{\text{MM. HG.}}{\text{L./MIN.}}\right)$	MEAN SYSTOLIC FLOW (C.C./SEC.)	PULMONIC VALVE AREA (CM.²)	PULMONIC VALVE DIAMETER (CM.)	RIGHT VENTRICULAR MAXIMUM POTENCY (KG./SEC.)	RIGHT VENTRICULAR WORK (KG.)			RIGHT VENTRICULAR STRAIN INDEX
																TO OVERCOME STENOSIS	USEFUL	TOTAL	
1	D.D.	Infundibular	80	1.63	230	2.71	1.66	169	20	18	55	89	.23	.54	.274	4.33	.70	5.03	7.2
2	L.M.	Valvular, I.A.S.D.	92	1.52	227	2.03	1.34	170	21	21	74	63	.16	.45	.185	3.51	.61	4.12	6.7
3	J.F.	Valvular, I.A.S.D.	61	2.05	408	4.66	2.27	120	20	17	22	186	.54	.83	.344	4.82	1.15	5.97	5.2
4	C.B.	Infundibular, I.A.S.D.	73	1.84	252	3.97	2.16	78	12	12	17	155	.60	.87	.205	2.74	.68	3.42	5.0
5	P.G.	Infundibular	62	1.75	313	4.83	2.76	115	20	18	20	231	.81	1.00	.496	4.06	1.25	5.31	4.2
6	E.S.	Valvular	82	1.40	224	3.98	2.84	64	17	12	12	127	.59	.87	.131	2.04	.69	2.73	4.0
7	R.M.	Infundibular, valvular, I.A.S.D., A.P.V.	87	1.23	241	3.51	2.85	35	10	8	7.1	139	.92	1.08	.073	.90	.41	1.31	3.2
8	M.C.	Valvular	90	1.28	170	4.96	3.88	38	12	10	5.2	205	1.13	1.20	.114	1.27	.71	1.98	2.8
9	C.F.	Valvular	94	1.96	368	12.80	6.52	55	22	18	2.6	485	3.18	2.02	.359	3.78	3.29	7.07	2.2
10	L.O.	Infundibular	90	1.37	321	4.95	3.61	26	18	11	3.0	190	1.90	1.56	.070	.73	.78	1.51	1.9
11	A.C.	Infundibular, valvular, A.P.V.	110	1.52	282	10.45	6.90	45	18	15	1.6	352	2.32	1.72	.104	1.74	2.25	3.99	1.8
12	J.M.	Infundibular, valvular	103	1.50	256	7.91	5.27	33	18	16	1.9	265	2.08	2.04	.076	1.34	1.82	3.16	1.7
13	M.S.	Valvular, I.A.S.D., A.P.V.	76	1.62	298	8.69	5.36	36	19	18	2.1	394	3.27	1.63	.146	1.53	2.25	3.78	1.7
14	N.C.	Infundibular, Valvular	99	1.44	181	9.70	6.75	28	20	17	.8	316	3.48	2.11	.050	.84	2.36	3.20	1.4
15	N.B.	Infundibular, valvular, I.A.S.D.	85	1.15	145	8.38	7.29	25	20	18	.7	318	6.00	2.76	.039	.48	2.17	2.65	1.2

I.A.S.D. = interauricular septal defect; A.P.V. = anomalous pulmonary vein draining into the right auricle.

TABLE II. COMPARATIVE VALUES OF HEMODYNAMIC, CLINICAL, RADIOLOGIC, AND ELECTROCARDIOGRAPHIC STUDIES

I.A.S.D. = interauricular septal defect; A.P.V. = anomalous pulmonary vein draining into the right auricle.

TABLE II. COMPARATIVE VALUES OF HEMODYNAMIC, CLINICAL, RADIOLOGIC, AND ELECTROCARDIOGRAPHIC STUDIES

CASE	NAME	SEX	AGE	TYPE OF PULMONIC STENOSIS AND ASSOCIATED MALFORMATION	RIGHT VENTRICULAR STRAIN INDEX	STENOSIS INDEX (SILBER ET AL.) $\left(\frac{\text{MM. HG}}{\text{L./MIN.}}\right)$	VALVULAR AREA ($CM.^2$)	CARDIAC INDEX $\frac{\text{L.}}{M.^2/\text{MIN.}}$	FUNCTIONAL CAPACITY	DYSPNEA	RADIOLOGIC EXAMINATION		ECG	
											RIGHT VENTRICLE	LUNG VASCULARIZATION	RIGHT VENTRICULAR STRAIN	RIGHT BUNDLE BRANCH BLOCK
1	D.D.	M	22	Inf.	7.2	55.0	.23	1.66	III	+++	++	Decreased	yes	no
2	L.M.	M	23	Valv., I.A.S.D.	6.7	74.0	.16	1.34	II	++	+	Decreased	yes	no
3	J.F.	F	23	Valv., I.A.S.D.	5.2	21.5	.49	2.27	II	++	+++	Decreased	yes	no
4	C.B.	M	51	Inf., I.A.S.D.	5.0	17.0	.60	2.16	II	++	++	Normal	yes	no
5	P.G.	M	17	Inf.	4.2	20.0	.81	2.76	I	0	+	Decreased	yes	no
6	E.S.	F	16	Valv.	4.0	11.8	.59	2.84	II	++	++	Decreased	yes	no
7	R.M.	M	12	Inf., Valv., I.A.S.D., A.P.V.	3.2	7.1	.92	2.85	I	0	++	Increased	yes	no
8	M.C.	F	32	Valv.	2.8	5.2	1.13	3.88	I	0	+	Decreased	yes	no
9	C.F.	M	21	Valv.	2.1	2.6	3.16	6.52	I	0	++	Decreased	no	no
10	L.O.	F	13	Inf.	1.9	4.0	1.89	3.61	I	0	0	Decreased	no	no
11	A.C.	F	15	Inf., Valv., A.P.V.	1.8	1.6	2.32	6.90	I	0	++	Increased	yes	yes
12	J.M.	F	26	Inf., Valv.	1.7	1.9	2.08	5.27	I	0	++	Normal	no	no
13	M.S.	M	18	Valv., I.A.S.D., A.P.V.	1.7	2.1	3.27	5.36	I-II	+	++	Increased	yes	no
14	N.C.	F	23	Inf., Valv.	1.4	.8	3.35	6.75	I	0	0	Normal	no	no
15	N.B.	F	12	Inf., Valv., I.A.S.D.	1.2	.7	6.00	7.29	I	0	++	Normal	yes	yes

Inf. = infundibular, Valv. = valvular, I.A.S.D. = interauricular septal defect, and A.P.V. = anomalous pulmonary vein draining into the right auricle.

In the cases with cardiac insufficiency (1 to 4, 6) the radiologic study revealed a right ventricular enlargement. In cases without cardiac insufficiency no relationship was found between the size and the strain index of the right ventricle. Generally speaking, the higher the strain index and the smaller the pulmonary valvular area, the clearer the pulmonary field. In Cases 7, 11, and 13 the increased pulmonary vascular shadows were due to the associated cardiac malformations.

In observations (Cases 1 to 8) with a higher strain index there were electrocardiographic evidences of right ventricular strain.

In Cases 11, 13, and 15 with a very low strain index, there was also some electrocardiographic evidence of right ventricular strain (Case 11) or right bundle branch block (Cases 13 and 15), but it has to be pointed out that they were cases with associated congenital malformations, such as interauricular septal defect or an anomalous drainage of a pulmonary vein into the right auricle.

DISCUSSION

The determination of the total work performed by the right ventricle in pulmonary stenosis without interventricular septal defect and relationship between the work to overcome the stenosis and the useful work provide another element to evaluate the myocardial functional condition.

The right ventricular strain index was found useful only in cases of pure pulmonary stenosis or when this condition was the most important cardiac malformation. In patients with other predominant cardiac lesions the right ventricular strain index is of no value in giving us an idea about the hemodynamic conditions, such as in our Cases 11, 13, and 15.

Through this paper we have considered three kinds of work done by the right ventricle: (a) total work, (b) the work performed to overcome the stenosis, and (c) the useful work. None of these per se can give an idea of the patient's clinical condition. Even when the first two are considered, the evaluation of the physical condition of the patient can be difficult, since it may occur that being the total work and the one performed to overcome the pulmonary stenosis very heavy, the useful work may be good enough as to maintain an adequate pulmonary flow (Case 9). On the contrary, if the total and useful work are related, that is to say, if the right ventricular strain index is obtained, it may give us an approximate idea of the clinical state of the patient, since, as the above-mentioned results show, there is a close relationship between them.

If we compare the strain index values obtained with those of the cardiac index (Fig. 1) it is proved that the higher strain index corresponds to the lower cardiac index. That there is a real concordance between them is demonstrated by the fact that the correlation index is $r = 0.75$ and $p < 1$ per cent.

The strain index has also a close relationship with the diameter of the pulmonic valve (Fig. 2) since the higher strain index corresponds to smaller valvular diameters. The correlation index $r = 0.84$ and $p < 1$ per cent proves this relationship.

Silber and associates[2] proposed the quotient of the pressure difference between the right ventricle and the pulmonary artery and the cardiac output as the stenosis index, considering it as the numerical expression of the dynamic meaning of pulmonary stenosis.

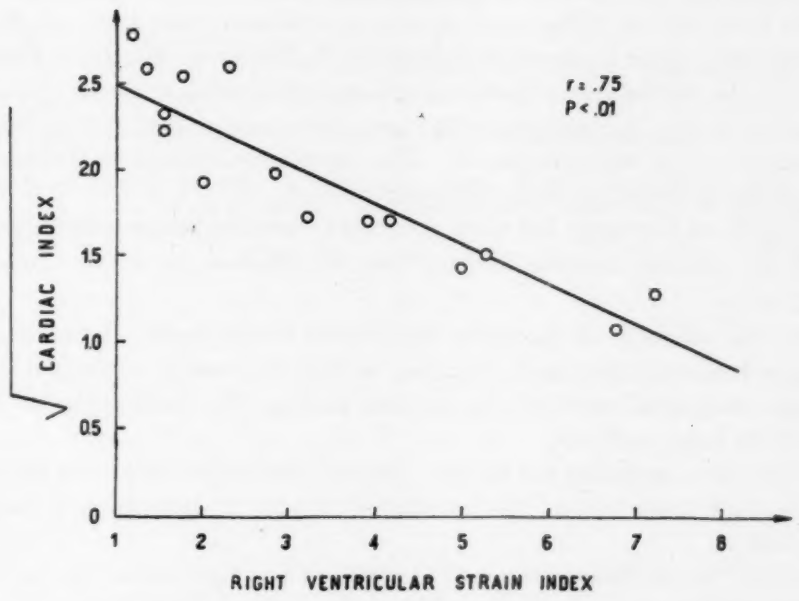

Fig. 1.—Relationship between the square root of the cardiac index and right ventricular strain index

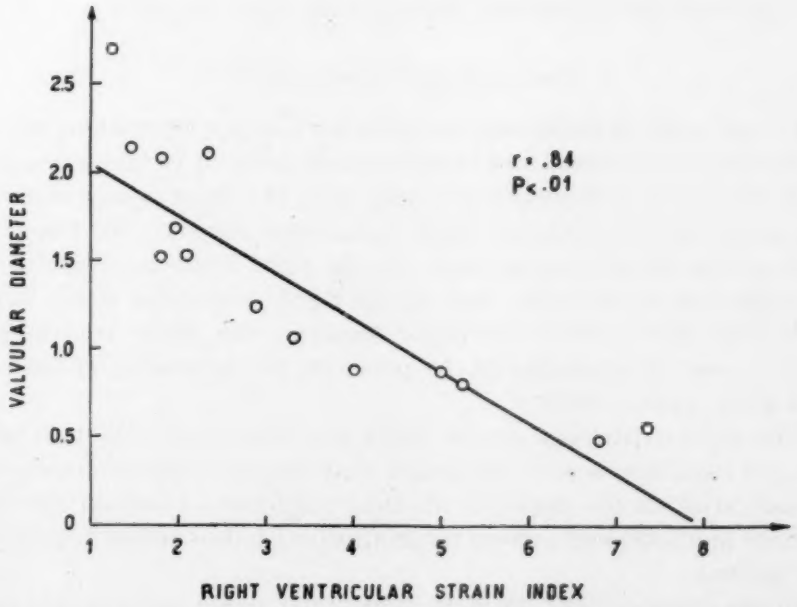

Fig. 2.—Relationship between pulmonary valvular diameter and right ventricular strain index.

In comparing the right ventricular strain index we have proposed with that of stenosis proposed by Silber and associates, it is seen that they nearly agree in the classification of the patients according to the degree of stenosis. However the right ventricular strain index showed a closer relationship with the clinical condition of the patient. A comparison between the strain index and the square root of the stenosis index was considered. The correlation index $r = 0.96$ and $p < 1$ per cent is clearly illustrative of this concordance.

The close relationship between the right ventricular strain index and the results of the clinical checkup having been established, we shall emphasize the following facts.

1. In the calculus of the right ventricular strain index, the cardiac output is not taken into consideration, avoiding in this way some occasional differences due to the emotional state of the patient during the cardiovascular catheterization and his body surface.

Furthermore, omitting the cardiac output, the strain index can be calculated without having made either the oxymetric study or the oxygen consumption determination.

2. After the cardiovascular catheterization has been done the right ventricular strain index can be calculated by using either Table III or the calculus

$$I.S. = 1 + \frac{\Delta P_{M_x}{}^{*}}{\text{mean pulmonary pressure}} \times 0.66.$$

The only two factors necessary for this equation are obtained by a continous tracing from the pulmonary artery to the right ventricle.

SUMMARY AND CONCLUSIONS

1. Fifteen cases of pulmonary stenosis with intact ventricular septum have been studied from the clinical and hemodynamic point of view; having calculated in all of them (a) the pulmonary valvular area, (b) the stenosis index of Silber and associates, (c) the maximum right ventricular potency, (d) the ventricular work to overcome pulmonary stenosis, (e) the right ventricular useful work, (f) the total right ventricular work, and (g) the right ventricular strain index.

2. A close relationship was found between the right ventricular strain index and the clinical condition of the patients, the narrowing of their valvular areas, and their cardiac index.

3. The right ventricular strain index was compared with that of stenosis by Silber and associates and it was found that they are approximately in accord in the classification of the patient's physical condition. However the right ventricular strain index showed a closer relationship with the cardiac functional capacity of the patient.

4. In the calculation of the right ventricular strain index it was possible to avoid the cardiac output, thus making the equation very simple and independent from the variations of the emotional conditions and the body surface of the patient.

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*ΔP_{M_x} means difference between right ventricular systolic and maximum pulmonary pressures.

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HEART DAMAGE IN DOGS SUBJECTED TO HYPOTHERMIA, CIRCULATORY ARREST, AND CARDIAC SURGERY

H. S. Samuli Sarajas, M.S., C.M.,* Åke Senning, M.D., and Jorge Kaplan, M.D.

Stockholm, Sweden

IT HAS been generally accepted by most investigators that systemic hypothermia, as employed in modern cardiac surgery, is a noninjurious and rather safe procedure. In his survey of the present status of hypothermia, Swan[1] states: ". . . above 20° C. no specific cellular pathology occurs within periods of several hours. The temperature range free of organic disturbances may even extend much lower, . . ." Recently, however, Sarajas[2] has presented gross and histologic evidence for myocardial damage in dogs subjected to hypothermia. In dogs autopsied at the onset of fatal cardiac crisis known to occur beneath a rectal temperature of 20° C., or at the termination of moderate (26° to 27.5° C.) or deep (21° to 22.5° C.) hypothermia of one to four hours' duration, he could demonstrate degenerative and early necrobiotic changes in the myocardial wall. On the other hand, in dogs sacrificed and autopsied at varying intervals after they had survived a moderate or deep hypothermia of the same duration, distinct myocardial necroses were detected, which in accordance with length of survival showed different stages of development and healing. These results corroborated the introductory studies of Sarajas and Nilsson,[4] which suggested that acutely induced hypothermia in dogs may, besides the liver and central nervous system, seriously affect the heart muscle.

The above observations were made in dogs subjected to hypothermia, without surgical interventions on the heart. The present study was undertaken to elucidate the pathology of the heart in dogs subjected during hypothermia to circulatory arrest, direct vision cardiac surgery, and routine measures of cardiac resuscitation.

MATERIAL AND METHODS

Eighteen young dogs, unselected as to breed or sex, and weighing from 1.8 to 17.5 kilograms were anesthetized with intraperitoneal Nembutal (30 mg. per kilogram). Dogs 1 to 11 received in addition intravenous ethyl alchohol (1 ml. 95 per cent ethyl alchohol in 2 ml. saline per kilogram), whereas dogs 17 and 18 were premedicated with subcutaneous Phenergan (2.5 mg. per kilogram). When the anesthesia was deep enough an endotracheal tube and a deep rectal thermocouple were inserted. Dogs 4, 6, 8, 9, 12, 13, 17, and 18

From the Departments of Surgery (Head: Clarence Crafoord, M.D.) and Pathology (Head: Nils Ringertz, M.D.), Sabbatsberg Hospital, and the Wenner-Gren Cardiovascular Research Laboratory (Heads: Carl Wegelius, M.D., and John Lind, M.D.,) and the Department of Pathology (Head: Sven Rubarth, V.M.D.), Royal Veterinary College, Stockholm, Sweden.

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*Present address: Kalevankatu 14 D., Helsinki, Finland.

were then cooled in a cold-air chamber (−10° to +3° C.), the other dogs in an ice bath (+4° to +8° C.). Below a rectal temperature of 30° C. the dogs were ventilated artificially by use of oxygen and the AGA-Crafoord spiropulsator.

Cooling was stopped at varying points between 29° and 17° C. and a thoracotomy was performed under aseptic conditions in the fourth right intercostal space. The azygos vein and both venae cavae were isolated and the pericardium opened. Noncrushing silk tourniquets were placed around the root of the azygos vein, superior and inferior venae cavae, aorta, and pulmonary artery; as a rule in this order. In dogs 1 to 11 (except dog 9), and in dogs 17 and 18 ventricular fibrillation was then induced by an electrical stimulus of 50 Ma. lasting 0.5 second, applied to the heart with silver electrodes 5 by 6 cm. in diameter. In dogs 12 to 15 the inflow-outflow occlusion soon resulted in spontaneous ventricular fibrillation, whereas in dog 16 a coordinated regular heart action continued during the period of occlusion and surgery. The time the heart was excluded from circulation, i.e., the duration of circulatory arrest, varied from 10 to 50 minutes (see Table I).

In dog 9 artificial respiration was not used during the cooling process. As a result respiratory and cardiac standstill occurred at a rectal temperature of 25° C. The heart was massaged, which resulted in ventricular fibrillation. After successful electrical defibrillation the dog was rewarmed.

In dogs 12 to 16 right atrial cardiotomy (RAC) with subsequent creation and closure of an interatrial septal defect was carried out.

In dogs 17 and 18 right ventricular cardiotomy (RVC) was performed and a piece of Ivalon sponge was sutured to the interventricular septum.

In the other experiments (dogs 1 to 11) no intracardiac surgery was performed during the time of circulatory arrest.

Accordingly, in all experiments, except that in dog 16, there existed ventricular fibrillation during the time the heart was excluded from circulation. To effect defibrillation the heart was massaged, and procaine hydrochloride (5 mg. per kilogram) and epinephrine (30 μ per kilogram) were injected into the right auricle. When the tone of the myocardium had been restored, defibrillation was accomplished by two or three electrical shocks of 1.5 to 2.5 amp. lasting 0.1 second. The rectal temperature was then raised 2° to 6°C. by use of diathermia, after which the thorax was closed, leaving a drainage tube. Rewarming was then completed using diathermia (dogs 1 to 11, 17, and 18), or immersion in a warm bath (dogs 12 to 16). At the termination of rewarming the dogs received 1,000,000 units of penicillin. The time which elapsed from the beginning of cooling to the end of rewarming varied in dogs 1 to 11 from six to eight hours, in dogs 12 to 18 from three to six hours.

Four of our eighteen experimental animals (dogs 1 to 4) succumbed during rewarming or in the early period following rewarming. The other fourteen dogs (dogs 5 to 18) survived the experimental period. They were intentionally sacrificed 4 to 125 days following the experiment. In all instances the dogs were immediately autopsied. Following gross examination multiple sections of different areas of the right and left sides of the heart were cut, fixed in 10 per cent formalin, and stained with scarlet red, hemalum-eosin, van Gieson stain, and Mallory's phosphotungstic acid hematoxylin.

TABLE I. ESSENTIALS OF THE EXPERIMENTAL PROCEDURES AND THE MORPHOLOGIC CARDIAC CHANGES IN DOGS UNDER HYPOTHERMIA SUBJECTED TO CIRCULATORY ARREST AND CARDIAC SURGERY, OR CIRCULATORY ARREST ALONE

DOG NO.	AGE	ANES-THESIA	INFLOW-OUTFLOW OCCLUSION	CARDIAC SURGERY	DEATH OR SACRIFICE	MORPHOLOGIC CARDIAC CHANGES
1	2 weeks	N + A	for 40′ at 17°C.	No	Death during rewarming	Early pericardial affection (Fig. 1. See details in text.). Foci of necrotic muscle fibers with early cellular reaction in the wall of the left ventricle (Fig. 6)
2	3 weeks	N + A	for 50′ at 22°C.	No	Death immediat. after rewarming	Early pericardial affection. Interstitial hemorrhages and foci of necrotic muscle fibers with early cellular reaction in the wall of both ventricles
3	1 year	N + A	for 30′ at 21°C.	No	Death 15 hours after rewarming	No evident pericardial affection. Areas of interstitial hemorrhage and edema, and focal myocardial necroses without evident reactive phenomena throughout the myocardial wall
4	2.5 months	N + A	for 25′ at 23.5°C.	No	Death 18 hours after rewarming	Early pericardial affection. Foci of necrotic muscle fibers with early cellular reaction located subendocardially in the papillary muscles of the left ventricle. Apparent early calcification of the necrotic muscle fibers (Fig. 7)
5	8 months	N + A	for 31′ at 19°C.	No	Sacrifice 4 days later	Fibrinous pericarditis. Focal areas of necrosis diffusely distributed throughout the myocardial wall. Calcified and sparcely infiltrated by mesenchymal cells showing mitotic figures (Fig. 8)
6	>1.5 years	N + A	for 22′ at 22°C.	No	Sacrifice 6 days later	Fibrinous pericarditis (Fig. 2). Areas of subendocardial necrosis in the wall of both ventricles. Infiltrated by mesenchymal cells showing frequent mitotic figures. The papillary muscles of the left ventricle particularly involved (Fig. 9)
7	1.5 years	N + A	for 30′ at 21°C.	No	Sacrifice 8 days later	Fibrinous pericarditis. Widespread areas of intense mesenchymal activation in the wall of both ventricles including the I-V septum (Fig. 10). Located for the most part subendocardially
8	8 months	N + A	for 30′ at 21°C.	No	Sacrifice 10 days later	Fibrinous pericarditis of adhesive type (Fig. 3). Small foci of necrosis infiltrated chiefly by mesenchymal cells. Located for the most part subendocardially in the wall of both ventricles including the I-V septum
9	>1.5 years	N + A	No occlusion (No art. resp. Card. standstill at 25°C.)	No	Sacrifice 11 days later	Fibrinous pericarditis. Minute foci of subendocardial necrosis in the anterior wall of the right ventricle including adjacent areas of the pulmonary conus. Calcified and surrounded by mesenchymal cells

10	3 months	N + A	for 30′ at 21°C.	No	Sacrifice 12 days later	Fibrinous pericarditis. Rather focal areas of necrosis in the anterior wall of the right ventricle (Fig. 13) and in the I-V septum. Calcified and infiltrated by mesenchymal cells. Moderate collagen formation
11	3 months	N + A	for 30′ at 20°C.	No	Sacrifice 12 days later	Fibrinous pericarditis of adhesive type. Widespread healing necroses in the papillary muscles of the left ventricle. The necrotic muscle material has been partially replaced by cellular scar tissue (Fig. 12)
12	6 months	N	for 11.5′ at 29°C.	RAC	Sacrifice 5 days later	Fibrinous pericarditis. Necrotic areas in the papillary muscles of the left ventricle, and in the wall of the I-V septum and the pulmonary conus. Calcified and infiltrated by mesenchymal cells showing frequent mitotic figures
13	6 months	N	for 11′ at 29° C.	RAC	Sacrifice 5 days later	Fibrinous pericarditis. Widespread areas of necrosis in the anterior wall of the pulmonary conus. Calcified and infiltrated by mesenchymal cells showing frequent mitotic figures
14	1.5 years	N	for 10′ at 27°C.	RAC	Sacrifice 8 days later	Fibrinous pericarditis. Necrotic areas of varying size diffusely distributed throughout the myocardial wall. Intense mesenchymal activation in the areas involved (Fig. 11)
15	9 months	N	for 11.5′ at 25.5°C.	RAC	Sacrifice 12 days later	Fibrinous pericarditis (Fig. 4). Myocardium uninvolved
16	1 year	N	for 11′ at 27°C. (No ventricular fibrillation; no resuscit. meas.)	RAC	Sacrifice 125 days later	No evidence of morphologic cardiac changes
17	6 months	Ph + N	for 14′ at 25°C.	RVC	Sacrifice 6 days later	Fibrinous pericarditis. Minute foci of necrosis in the septal papillary muscles and in the papillary muscles of the left ventricle. Calcified and sparcely surrounded by mesenchymal cells
18	6 months	Ph + N	for 13′ at 26°C.	RVC	Sacrifice 39 days later	Healing pericarditis (Fig. 5). Subepicardial and subendocardial necroses in the wall of the pulmonary conus. Calcified and encapsulated by fibrous coat (Fig. 14)

Abbreviations: N = Nembutal; A = ethyl alcohol; Ph = Phenergan (promethazine hydrochloride); RAC = right atrial cardiotomy; RVC = right ventricular cardiotomy.

OBSERVATIONS

The data of the essential experimental procedures as well as the morphologic cardiac alterations in our dogs are summarized in Table I. The table reveals that both pericardium and myocardium were affected in the great majority of our dogs subjected during hypothermia to circulatory arrest and cardiac surgery, or circulatory arrest alone. In the following the pericardial and myocardial changes will be detailed separately.

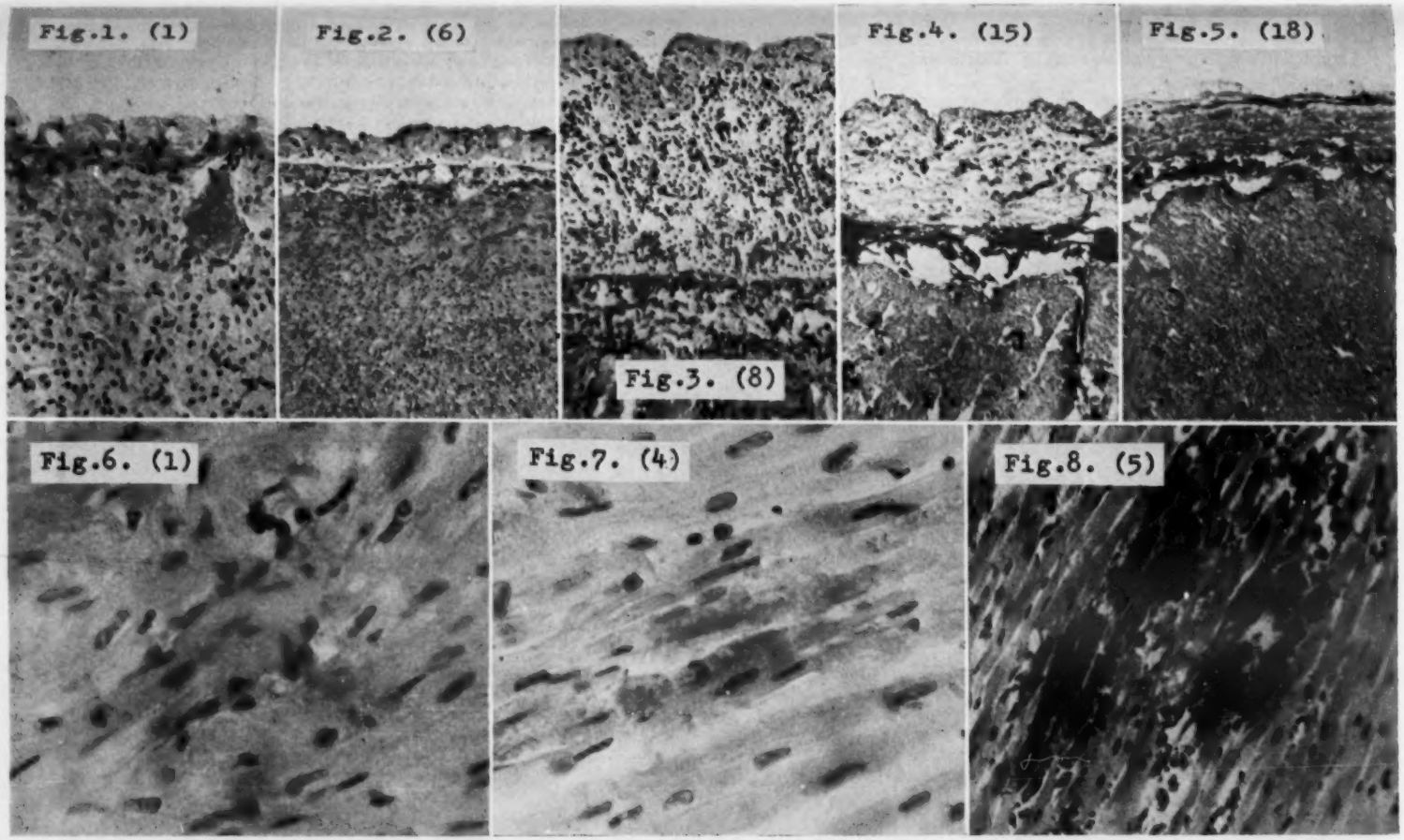
Pericardial Changes.—In all but two cases (dogs 3 and 16) the autopsy revealed localized pericardial involvement consisting mainly of a typical pattern of fibrinous pericarditis of varying stages.

In dogs that succumbed during rewarming, or in the early period following rewarming (dogs 1 to 4), the visceral pericardium, when involved (dogs 1, 2, and 4), had lost its gloss and was slightly rough and granular in appearance. Histologically, there were engorgement of the epicardial vessels, loss of the lining mesothelial cells, and a scanty deposition of fibrin on the epicardial surfaces. Enmeshed were a few polymorphonuclears and lymphocytes. There were concomitant changes in the muscle fibers just beneath the affected epicardium consisting principally of hyaline necrosis with slight reactive phenomena (Fig. 1).

In dogs sacrificed and autopsied at varying intervals after the experiment (dogs 5 to 18) a more marked deposition of fibrin became apparent on the epicardial surface. The fibrin was arranged in smaller or larger clumps and villi, occasionally in the form of adhesions between the parietal and visceral pericardium (dogs 8 and 11). The histologic picture changed according to length of survival. In dogs sacrificed four to eight days after the experiment (dogs 5 to 7, 12 to 14, and 17) the fibrin masses covering the epicardial surface and the outer layer of the underlying myocardium were more intensely infiltrated by polymorphonuclears and lymphocytes (Fig. 2). In occasional cases the subepicardial muscle fibers showed fatty degeneration (dogs 5 and 13). Then, various stages of organization became apparent (dogs 8 to 11, 15, and 18), i.e., the fibrin masses including the adjacent subepicardial muscle layers were replaced by vascular fibroblastic granulation tissue (Fig. 3), becoming progressively poorer in cells and richer in collagenous fiber material (Figs. 4 and 5).

Myocardial Changes.—In all but two cases (dogs 15 and 16) there were concurrent morphologic changes in various layers of the myocardial wall, distant from the affected epicardium and the sutured wounds made in association with cardiac surgery.

In experiments with fatal termination during rewarming or in the early period following rewarming (dogs 1 to 4), there was, except occasional subendocardial hemorrhages (dog 2), no gross evidence of myocardial involvement. In contrast, histologic examination revealed in all these cases foci of hyaline (dogs 1 to 4) or granular (dog 4) myocardial necrosis in three cases associated with slight inflammatory reaction (dogs 1, 2, and 4). The infiltrating cells, small in numbers, consisted chiefly of lymphocytes and polymorphonuclear leukocytes (Figs. 6 and 7). Besides these alterations areas of interstitial hemorrhage (dogs 2 and 3) and edema (dog 3) could be demonstrated in the myocardial wall.



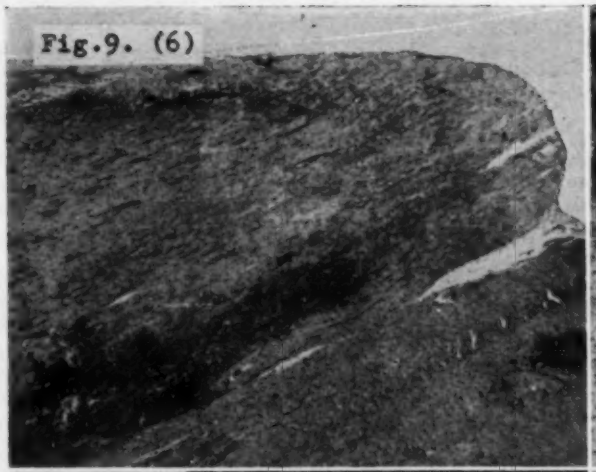
Figs. 1 to 5.—These figures illustrate different stages of development and healing of localized fibrinous pericarditis in dogs subjected during hypothermia to circulatory arrest and cardiac surgery, or circulatory arrest alone. The dogs died during rewarming (Fig. 1) or were sacrificed at increasing intervals following survival (Figs. 2 to 5). The numbers in parentheses indicate the number of dogs. See details in text and Table I.

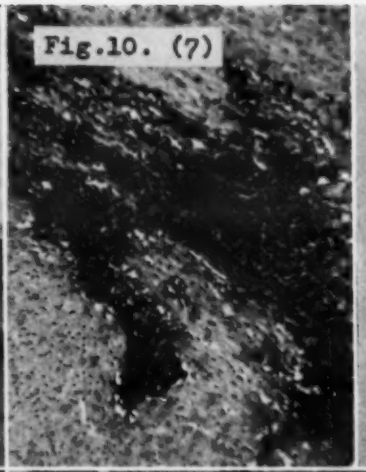
Figs. 6 to 8.—These figures show coexisting pathologic changes in various areas of the myocardial wall.

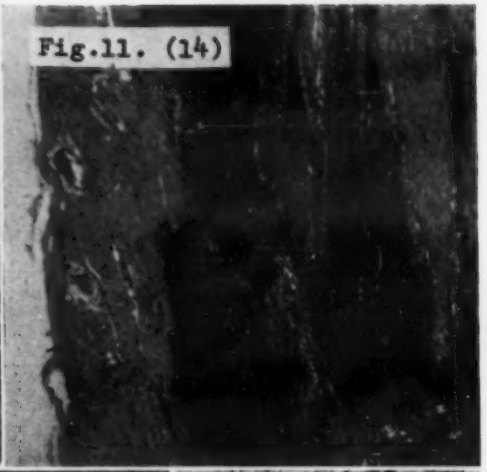
Fig. 6.—Focal myocardial necrosis of hyaline type in the left ventricular wall infiltrated by a few polymorphonuclears and lymphocytes. The dog succumbed during rewarming.

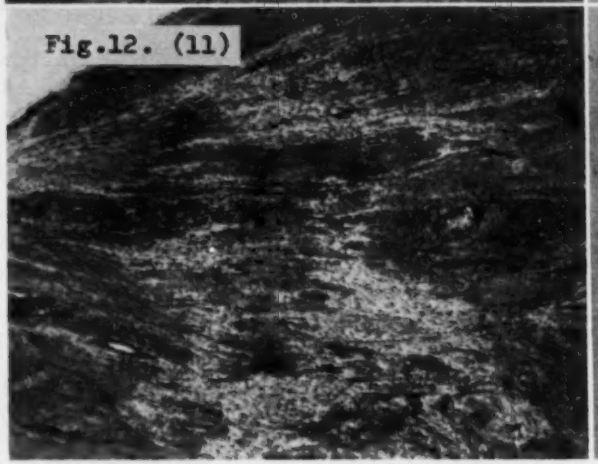
Fig. 7.—Focal area of hyaline and granular myocardial necrosis with a few emigrated polymorphonuclears and lymphocytes located subendocardially in the anterior papillary muscle of the left ventricle. The granularity, basophilic in nature, suggests early calcification. The dog died eighteen hours following rewarming.

Fig. 8.—An area of the interventricular septum showing myocardial necrosis with intense calcification and slight mesenchymal activation. The dog was sacrificed four days after the experiment.









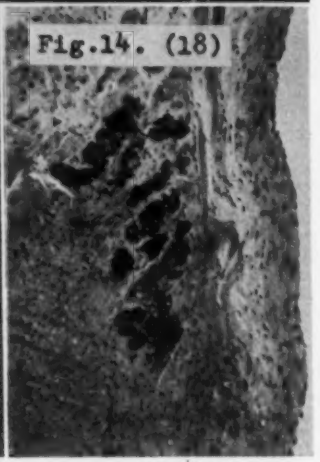


Fig. 9.—This figure shows apical portion of the posterior papillary muscle of the left ventricle in a dog sacrificed six days after the experiment. The necrotic areas are infiltrated by mesenchymal cells.

Figs. 10 and 11.—These figures illustrate areas of intense mesenchymal activation in the interventricular septum and right ventricular wall near the apex. Both dogs were sacrificed eight days after the experiment.

Fig. 12.—Apical portion of the anterior papillary muscle of the left ventricle. The necrotic muscle fibers have been partially replaced by cellular scar tissue. The dog was sacrificed twelve days following the experiment.

Figs. 13 and 14.—These figures show foci of subepicardial and subendocardial necrosis, respectively, in the anterior wall of the pulmonary conus. The necrotic calcified muscle fibers have been encapsulated by cellular (Fig. 13) or fibrous (Fig. 14) scar tissue. The dogs were sacrificed twelve and thirty-nine days after the experiment, respectively.

In dogs sacrificed at varying intervals after the experiment (dogs 5 to 18), there were, except dogs 15 and 16, distinct lesions in the heart muscle, variable in size, location, and distribution. When extensive enough, they became grossly apparent as rather sharply delineated yellowish-gray spots. However, in the majority of cases they could clearly be demonstrated only by histologic examination. The histologic picture of the lesions was characterized mainly by calcified myocardial necroses at different stages of development and healing (Figs. 8 to 14). In dogs sacrificed four to eight days following the experiment (dogs 5 to 7, 12 to 14, and 17), there was, instead of the slight acute inflammatory reaction seen in the earlier lesions, mesenchymal activation in the involved areas, i.e., the necrotic muscle material was infiltrated predominantly by mesenchymal cells showing frequent mitotic figures. The amount of the activated mesenchyme and the intensity of calcification in the muscle fibers showed generally inverse relationship (Figs. 8 to 11). In dogs sacrificed ten to thirty-nine days following the experiment (dogs 8 to 11 and 18), further advanced stages of organization with ultimate cicatrization became apparent. The necrotic muscle material had been in varying degree replaced by cellular (Fig. 12) or fibrous scar tissue. At the same time, the calcified myocardial necroses had been encapsulated by a thin coat of fibrous scar tissue with progressive collagen formation (Figs. 13 and 14).

The lesions described above were essentially restricted to the ventricular myocardium, whereas there was little evidence of atrial involvement. Independent of the experimental procedures, the lesions could be detected in any portion of the ventricles including the interventricular septum. The papillary muscles, the apical portions, and the anterior wall of the right ventricle including the wall of the pulmonary conus seemed to disclose alterations with somewhat greater frequency. The subendocardial muscle layers were particularly involved. However, there was consisently a thin layer of surviving myocardium along the endocardial surface. All stages from the occurrence of a single or a few affected areas to the rather diffuse myocardial damage were noted.

DISCUSSION

In the present experiments eighteen dogs in hypothermia were subjected to circulatory arrest (except dog 9), complicated or uncomplicated by intracardiac surgery. The experimental procedures included additionally routine measures of cardiac resuscitation, such as cardiac massage and electric shock application (except dog 16). In fifteen of these eighteen cases autopsy, performed at varying intervals after the experiment, revealed pericardial and myocardial damage consisting of localized fibrinous pericarditis and necrobiotic myocardial changes, respectively. In one case there was myocardial affection without coexisting pericardial involvement (dog 3), and in one case the pericardium was affected, the myocardium being intact (dog 15). In only one case could neither pericardial nor myocardial involvement be demonstrated (dog 16). Such an incidence of pathologic cardiac changes in young and apparently healthy dogs makes it evident that the lesions are pathogenetically related to the essential experimental procedures of the present study. This

sacrificed twelve and thirty-nine days after the experiment, respectively.

suggestion is further supported by the fact that the lesions showed different stages of development and healing in accordance with the length of survival.

The pericardial damage in our dogs, involving even the outer subepicardial muscle layers, is obviously ascribable to the measures of cardiac resuscitation, including manual massage and electric shock application. This assumption is substantiated by the recent studies of Tedeschi and White.[3] These workers demonstrated that manual compression on the fibrillating heart in anesthetized normothermic dogs may result in supepicardial necroses. Moreover, electric shock defibrillation and subsequent cardiac massage resulted in more severe changes consisting initially of fibrinous hemorrhagic exudation, and later of fibrous tissue formation and pericardial adhesions. The underlying myocardium revealed first necrosis and inflammatory reaction, and finally superficial fibrosis.

The above pathologic cardiac changes arising from cardiac massage and electric shock defibrillation alone were restricted to the pericardium and/or the outer subepicardial muscle layers. In contrast, in the present experiments the myocardial alterations extended even to the deeper layers of the myocardial wall and were in many cases found predominantly, or solely, in the subendocardial muscle layers. It is to be recalled, however, that in the previous investigations on cardiac pathology resulting from hypothermia per se[2,4] the pericardium was consistently unaffected, whereas the myocardium showed pathologic changes similar in every characteristic to those revealed by the present experiments. It is, therefore, evident that, as regards their pathogenesis, the myocardial changes in our dogs are chiefly related to the cooling procedure itself.

For the present, not much is known about the pathogenetic mechanisms leading to irreversible myocardial damage in association with hypothermia. The patchy character of the lesions and the consistent existence of a thin layer of surviving myocardium along the endocardial surface suggest that they arise from focal disturbances in the myocardial blood or oxygen supply. However, the present and earlier[2,4] investigations revealed no direct evidence of thrombotic or embolic phenomena in the coronary vascular bed. Admittedly, in some of the earlier experiments[2,4] the wall of the myocardial arterioles showed thickening with resultant narrowing of the lumen, but such vascular changes might have been incidental and without pathogenetic significance, since they were not seen in all cases with myocardial damage. Recently, however, Gelin and Löfström,[5] confirming the earlier observations of Bigelow and associates,[6] have shown that during progressive cooling increasing aggregation of red cells takes place in the peripheral vascular bed, resulting ultimately in complete cessation of the capillary blood flow. Thus, the myocardial lesions revealed by the present studies might represent true myocardial infarctions. This view is supported by the fact that the speed of development and healing as well as the gross and histologic characteristics of the lesions correspond to those in experimentally produced myocardial infarctions in dogs.[7] Moreover, in hypothermia, the blood pressure being markedly lowered,[6] the pressure within some terminal branches of the coronary vascular tree may fall below a critical level (the "critical closing pressure"[8]) with resultant closure of the vascular lumina, and subse-

quent patchy myocardial damage. This may occur particularly in the subendocardial compartments of the coronary vascular bed, which would explain the frequent incidence of the subendocardial injury pattern in the present studies. The myocardial strain during cooling, as suggested by the autopsy findings[4] and the serial heart volume determinations during cooling,[9] may be a contributing factor, since the thinnest and most distensible portions of the ventricular myocardium, including the papillary muscles, the apical portions, and the anterior wall of the right ventricle, seemed to be particularly affected. The possible pathogenetic role of relative myocardial hypoxia remains to be solved. It has been suggested that in hypothermia there exists no failure in the myocardial oxygenation,[10,11,12] but rather in the ability of the heart muscle to convert aerobic energy into useful work.[12] This might hold true in the stable period of hypothermia. However, tachycardia, for example, frequently accompanying the early cooling period as well as the shocklike state of rewarming, may well give rise to relative myocardial hypoxia. At any rate, it may be noted that myocardial hypoxia of different origin may result in patchy myocardial changes[13,14] similar to those revealed by the present studies. When ventricular fibrillation with associated coronary circulatory arrest is sustained for longer periods, as in the particular experimental conditions of the present study, the heart muscle is probably suffering from hypoxia. Tedeschi and White[3] also found myocardial necroses in dogs, in which ventricular fibrillation, lasting up to twenty minutes, was the essential experimental procedure.

Focal areas of injury in the myocardial wall naturally result in loss of the functioning muscle units. When extensive enough or diffusely distributed, such patchy lesions may seriously impair myocardial efficiency. This may cause fatal cardiac failure even without the contribution of coexisting disturbances in the cardiac rhythm.[15] On the other hand, areas of myocardial injury may initiate conduction disturbances, premature beats, and ventricular fibrillation,[15,16] known to appear and result in fatal termination during the process of cooling or rewarming.[6,17,18] These mechanisms may contribute to each other, and in the presence of any additional stress to the heart, such as surgical trauma and the alterations in various physiologic equilibria known to accompany the cooling and rewarming process,[6,18,19] there exist predisposing conditions for supervention of fatal cardic failure. The pericardial damage, as seen in our dogs, is apparently of lesser functional significance, especially early. However, there may be a risk of constriction later on.

The results reported here as well as the earlier observations[2,4] tend to substantiate the assumption that some pathologic cardiac changes may cause or contribute to the fatal termination occurring with varying frequency in association with experimental hypothermia complicated[20-23] or uncomplicated[6,17,18] by cardiac surgery. Whether or not the same pattern of pathologic cardiac changes occurs in human beings subjected to similar surgical procedures is not known at present.

SUMMARY

Eighteen young mongrel dogs at a rectal temperature of 29° to 17° C. were subjected to circulatory arrest lasting 10 to 50 minutes. During the period of circulatory arrest intracardiac surgical maneuvers were performed on seven dogs. Four of the eighteen dogs succumbed during rewarming or in the early period following rewarming. The other fourteen dogs were intentionally sacrificed at varying intervals following the experimental procedure.

In all but one case autopsy revealed pathologic cardiac alterations consisting of localized fibrinous pericarditis, and of necrobiotic myocardial changes, variable in size, location, and distribution. A pathogenetic relationship of these cardiac changes to the experimental procedures used has been evidenced. The ultimate etiology of the lesions and their possible functional significance are discussed.

The present results, supported by the earlier observations, tend to substantiate the assumption that injury to the heart may be a factor causing or contributing to fatal termination in association with experimental hypothermia complicated or not by cardiac surgery.

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DISPLACEMENT, VELOCITY, AND ACCELERATION BALLISTOCARDIOGRAMS AS REGISTERED WITH AN UNDAMPED BED OF ULTRALOW NATURAL FREQUENCY

III. The Normal Ballistocardiogram

Maurice B. Rappaport, E.E.

Boston, Mass.

THE dynamic principles[2] which were discussed in relation to ballistocardiography indicate that ballistocardiograms registered on normal subjects with an undamped bed of ultralow natural frequency should differ to a considerable degree from those registered with the Starr, Nickerson, or Dock techniques. In order to investigate this phase of the subject and to evaluate the normal ballistocardiogram, approximately 100 normal adult subjects between the ages of 18 and 76 years were studied with undamped and slightly damped beds[3] which met the minimal ballistocardiographic criteria previously set forth.[2]

In Fig. 1 may be seen acceleration, velocity, and displacement ballistocardiograms simultaneously registered with the carotid pulse on a normal 36-year-old man shortly after being placed on the bed in a supine position. The bed was undamped, weighed 4 pounds, and had a natural frequency of 0.25 cycles per second. Record A is labeled as acceleration or force because, in a ballistic system such as used here, the configuration of the acceleration and force ballistocardiograms is similar.[2] That is,

$$F = \frac{W}{g} \cdot a \qquad (1)$$

where F = force in pounds,
W = body weight in pounds,
g = acceleration of gravity = 32.16 ft. per second per second, and
a = body acceleration in feet per second per second.

For a particular subject during a ballistocardiographic test, the body weight stays constant no matter what the magnitude of the cardiovascular forces or the resultant body accelerations may be. Therefore, the ballistocardiograms which represent the force acting on the body and the acceleration the body acquires as a result of the applied force are of similar configuration, except that they are evaluated differently in that the instantaneous force is expressed in pounds and the instantaneous acceleration is expressed in feet per second per second.

From the Ballistocardiographic Laboratory, Cardiology Department, Massachusetts General Hospital, Boston, Mass.

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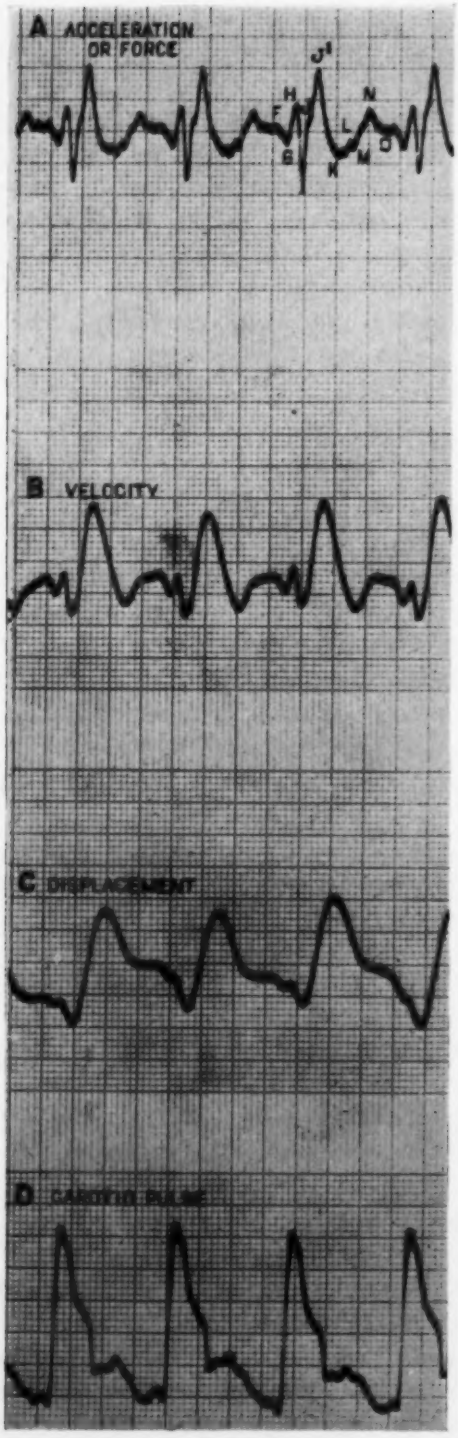

Fig. 1.—Characteristic appearance of the acceleration or force (*A*), velocity (*B*), and displacement (*C*) ballistocardiograms simultaneously registered with the carotid pulse (*D*) of a normal subject as obtained with an 0.25 cycle per second undamped bed weighing 4 pounds. The paper speed is 25 mm. per second.

As had been predicted from the theory,[2] the ballistocardiograms of Fig. 1 show no evidence of the presence of the 4 to 5 cycle per second body resonance vibrations which normally start in systole and carry over into diastole as a diminuendo sinusoidal oscillation when the free body movements are impeded by the support. Not a single subject tested showed any evidence of this form of distortion.

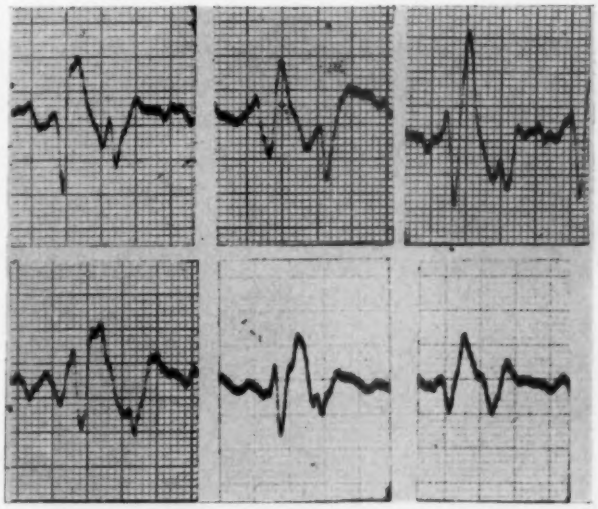

Fig. 2.—Acceleration or force ballistocardiograms of six normal subjects which illustrate the type of pattern which is generally obtained. The paper speed is 25 mm. per second.

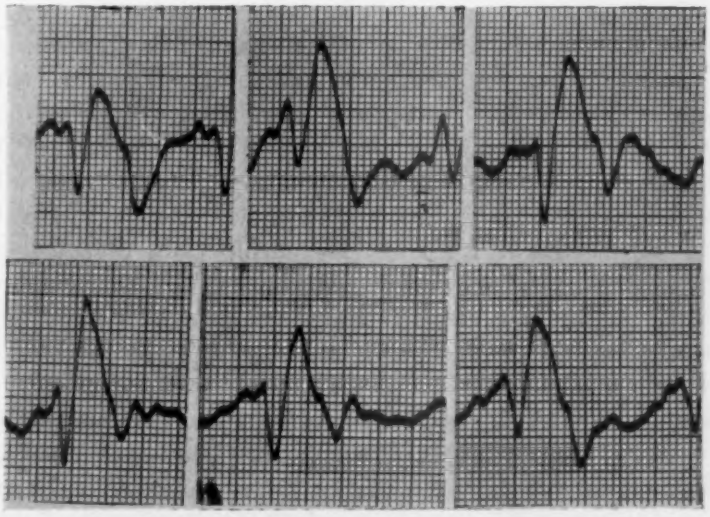

Fig. 3.—Velocity ballistocardiograms of six normal subjects to illustrate the type of pattern which is generally obtained. The paper speed is 25 mm. per second.

In Fig. 2 may be seen six acceleration ballistocardiograms of normal subjects to illustrate the normal variations in configuration. Fig. 3 illustrates the normal variations that are seen in the velocity ballistocardiogram and Fig. 4 shows the normal variations in the displacement ballistocardiogram. None of the eighteen

subjects in Figs. 2, 3, and 4 show evidence of the presence of diminuendo sinusoidal body oscillations. Because of the absence of these parasitic oscillations, masking effects upon the cardioballistic movements of the body are not present, and as a result, the ballistocardiographic configuration assumes a complex form with definite relationship to other cardiovascular events. Although the pattern is complex, the configuration varies to a surprisingly small degree in normal subjects.

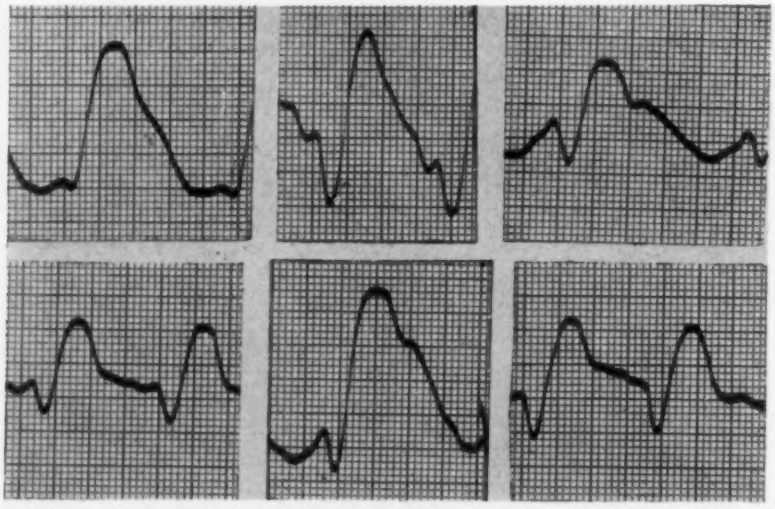

Fig. 4.—Displacement ballistocardiograms of six normal subjects to illustrate the type of pattern which is generally obtained. The paper speed is 25 mm. per second.

In order to clearly describe the normal acceleration, velocity, and displacement ballistocardiograms and show their relationship to other cardiovascular events, a composite sketch was made (Fig. 5) relating the three forms of body motion to the carotid pulse and the phonocardiogram. The latter cardiovascular events were chosen as they are mechanical events which have been most valuable in timing the ballistic events during the cardiac cycle. Other cardiovascular events such as the electrocardiogram, apex cardiogram, the various peripheral pulses, and the venous pulse have been used and will be referred to. At no time, in a normal subject, was the electrocardiogram necessary for orientation purposes as is customarily done when using the Starr and Dock techniques. If the rate and rhythm are normal, the events in each cardiac cycle are distinct and completely obvious as in Fig. 1. In some abnormal conditions which will not be discussed here, the electrocardiogram is helpful. The venous pulse which was taken over the internal jugular bulb cannot be consistently registered when the subject is in a supine position as is required for ballistocardiography. The satisfactory venous pulse tracings which were obtained did show a consistent and definite relationship to the ballistocardiogram and were helpful when satisfactorily recorded. The phonocardiogram, especially in the normal subject, is an extremely helpful reference, as most of the mechanical events in the cardiac cycle are represented. In certain cardiac abnormalities, murmurs may mask some of the mechanical events in the phonocardiogram.

OBSERVATIONS

Acceleration F Wave.—A coarse positive wave of low amplitude is registered in most normal acceleration ballistocardiograms which is called F in Figs. 1 and 5. The F wave occurs simultaneously with the atrial sound in the phonocardiogram (Fig. 5), between the electrocardiographic P and Q waves, and coincides with the atrial wave of the apex cardiogram and the a wave of the venous pulse. These cardiovascular interrelationships suggest that the acceleration or force F wave occurs during atrial systole. The fact that the F wave is always positive would further suggest that it represents the recoil forces during atrial systole, which produces a headward body movement.

Velocity $\dot{F}$ Wave.—The normal velocity $\dot{F}$ wave (Fig. 5) appears as a coarse, positive wave of low amplitude. When the velocity and acceleration ballistocardiograms are simultaneously registered, the velocity $\dot{F}$ wave registers later than the acceleration F wave. This temporal or phase displacement is a normal phenomenon, as has been shown in the theoretical discussion[2] where the phase angles for displacement, velocity, and acceleration were related to the ratio of the applied frequency to the natural frequency for various degrees of damping. It was further shown graphically[2] that, when no damping is present and phase distortion is absent, the graphic complex which represents bed or body acceleration leads the velocity complex of similar origin by 90 degrees and the displacement complex by 180 degrees. This graphic relationship conforms with the mathematical expressions for motion[3] which state that the acceleration at any instant of time is the first derivative of velocity with 90-degree phase displacement and the second derivative of displacement with 180-degree phase displacement.

Displacement F Wave.—A displacement F wave is registered in most normal subjects, which can readily be seen in Figs. 1 and 5. The displacement F wave occurs simultaneously with the acceleration F wave but the polarity is negative.

It should now be apparent why the nomenclature used in Fig. 5 was chosen. All registered complexes of the same cardiovascular origin in the acceleration and displacement ballistocardiograms are synchronous but of opposite polarity, whereas the velocity complex is temporally displaced. As a result, all velocity waves are indicated with a dot above the letter to show that it is the temporally displaced velocity complex which corresponds to the wave with the same letter in the acceleration and displacement ballistocardiograms which are synchronous.

Acceleration G Wave.—The acceleration G wave (Fig. 5) is most always registered in the normal subject. It is a low amplitude negative wave and always registers synchronously with the second component of the first heart sound[4,5] which represents the closure of the A-V valves.

Velocity $\dot{G}$ Wave.—The velocity $\dot{G}$ wave (Fig. 5) is usually well registered but with low amplitude in the normal subject and temporally lags behind the acceleration G wave.

Displacement G Wave.—The displacement G wave (Fig. 5) is generally well seen in the normal subject with a positivity of low amplitude but synchronous with the acceleration G wave.

Acceleration H Wave.—In every normal subject, the acceleration H wave (Fig. 5) seems to show a gradual rise from the negative G wave with an abrupt drop off at H. The abrupt drop off always registers simultaneously with the

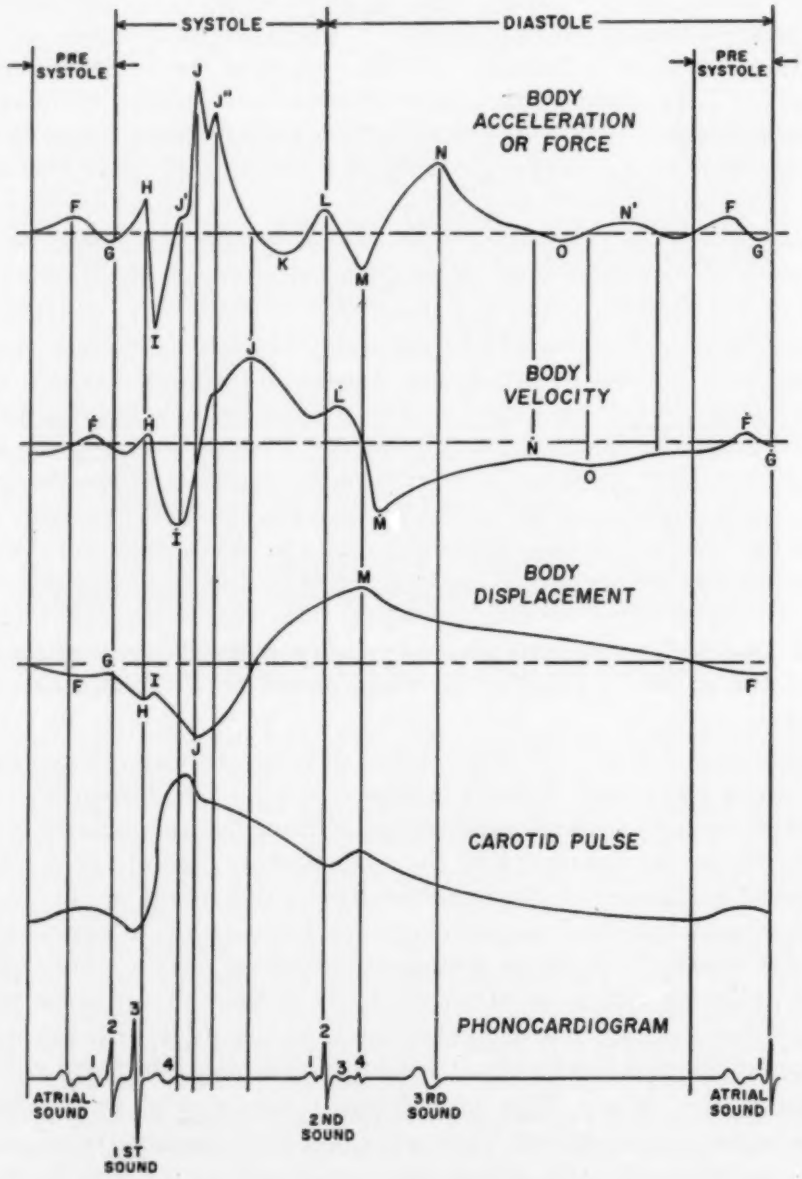

Fig. 5.—A composite sketch which relates the three forms of body motion to the carotid pulse and the phonocardiogram.

third component of the first heart sound[4,5] which represents the time the semilunar valves open.

Velocity $\dot{H}$ Wave.—The velocity $\dot{H}$ wave (Fig. 5) is generally registered but with rather low amplitude and temporally lags behind the acceleration H wave.

Displacement H Wave.—The displacement H wave (Fig. 5) is generally noticeable and registers with a negative low amplitude and occurs simultaneously with the acceleration H wave but with opposite polarity.

Acceleration HIJ′ Wave.—The acceleration HIJ′ wave (Fig. 5) in the normal subject is a deep negative spike. It commences at the time the semilunar valves open (third component of the first heart sound) and with the onset of the carotid pulsation. The HIJ′ wave represents a footward force and may very well be the recoil during the primary ventricular ejection phase of the cardiac cycle.

Velocity $\dot{H}\dot{I}\dot{J}'$ Wave.—The trough of the $\dot{H}\dot{I}\dot{J}'$ wave (Fig. 5) is most always well registered with a temporal lag with respect to the acceleration HIJ′ wave. $\dot{J}'$ can rarely be distinguished in the velocity ballistocardiogram.

Displacement HIJ′ Wave.—The HI segment of the displacement HIJ′ wave (Fig. 5) can generally be seen with a very low amplitude positive slope and J′ is not distinguishable.

Acceleration IJ′JJ″ Wave.—The acceleration IJ′JJ″ wave (Fig. 5) occurs during the maximum systolic ejection phase of the cardiac cycle. The J′ notch always seems to register simultaneously with the maximum peak of ventricular ejection shown in the carotid pulse. J′ occurs in some subjects slightly above the base line as shown in Fig. 5 and in others further above; in some normal persons the J′ notch may not be distinguishable. The amplitude and position of the J′ notch above the baseline varies to some extent with the phase of respiration.

The J wave always seems to register simultaneously with the abrupt change of slope in the carotid pulse just after the maximum ejection phase. The J″ notch consistently occurs at the end of the short plateau in the carotid pulse. The J″ notch may vary its distance above the baseline with respiration and in some subjects may not be registered. The mechanism of the production of the J′ and J″ notches is not clear although they seem to be related to the abrupt changes in blood flow during the maximum ejection phase. The J′ and J″ notches are made up of vibration components at least as high as 40 cycles per second.

Velocity $\dot{I}\dot{J}'\dot{J}\dot{J}''$ Wave.—The detail that is present in the acceleration IJ′JJ″ wave (Fig. 5) is missing in the velocity $\dot{I}\dot{J}'\dot{J}\dot{J}''$ wave which registers as a coarse positive wave which temporally lags behind the acceleration IJ′JJ″ wave.

Displacement IJ′JJ″ Wave.—The displacement IJ′JJ″ wave (Fig. 5) is a moderately deep negative wave which registers simultaneously with the positive acceleration IJ′JJ″ wave. The J′ and J″ notches, even though well registered in the acceleration ballistocardiogram, are never distinguishable in the displacement ballistocardiogram.

Acceleration K Wave.—The acceleration K wave (Fig. 5) consistently registers as a sluggish coarse wave of minimal negative amplitude. In the acceleration ballistocardiogram it appears as the terminal phase of reduced ejection. After the maximum ejection phase IJ′JJ″, reduced ejection commences as is indicated in the carotid pulse and the progressively sluggish J″ K segment in the acceleration ballistocardiogram.

Velocity $\dot{K}$ Wave.—Does not register.

Displacement K Wave.—Does not register.

Acceleration L Wave.—The acceleration L wave (Fig. 5) is generally a low amplitude positive wave which may have some sharp spikes or high frequency vibrational components superimposed upon it. It registers simultaneously with the second component of the second heart sound[4] in the phonocardiogram, which is the instant of time during the cardiac cycle the semilunar valves close.

Velocity $\dot{L}$ Wave.—The velocity $\dot{L}$ wave (Fig. 5) is generally noticeable as a low amplitude notch on the $\dot{J}\dot{M}$ segment in the form of a positive wave which lags behind the acceleration L wave.

Displacement L Wave.—Does not register.

Acceleration M Wave.—The acceleration M wave (Fig. 5) is a low amplitude negative wave which may have some sharp spikes or high frequency vibrational components superimposed upon it. It registers simultaneously with the fourth component of the second heart sound[4] in the phonocardiogram, which is the instant of time during the cardiac cycle the A-V valves open. The valley in the apex cardiogram just prior to the rapid inflow of the blood into the ventricles occurs simultaneously and is very helpful in timing this event.

Velocity $\dot{M}$ Wave.—The velocity $\dot{M}$ wave registers as a coarse negative wave without the superimposed high frequency vibrations frequently found in the acceleration M wave. There is a temporal delay in the velocity $\dot{M}$ wave as related to the acceleration M wave.

Displacement M Wave.—The displacement M wave is a very coarse positive wave which attains its maximal amplitude in most normal subjects at approximately the time the A-V valves open. This temporal relationship does not always hold true and may be a coincidence in most normal subjects. The displacement M wave is actually a composite wave which represents body displacement as a result of forces acting in the headward direction probably created by the ejection of blood into the vascular system and representing a mass displacement of blood in the body. Whatever wave is produced during the opening of the A-V valves in the displacement ballistocardiogram can only be considered as a contributing wave which is graphically summated.

Acceleration N Wave.—The acceleration MN segment is a steep positive slope of moderate magnitude. The third heart sound registers during the latter part of the MN segment and terminates at approximately the terminal portion of the segment. This indicates that the MN segment is related to the rapid inflow of blood into the ventricles. The fact that the MN segment has a positive slope which represents headward forces further indicates that it is due to the recoil action during rapid inflow and not forces created by the blood impacting in the ventricles which would be footward with resultant negativity. The NO segment is a sluggish or gradual negative slope toward the baseline.

Velocity $\dot{N}$ Wave.—No distinct $\dot{N}$ wave (Fig. 5) is noticeable in the normal velocity ballistocardiogram.

Displacement N Wave.—No distinct N wave (Fig. 5) is noticeable in the normal displacement ballistocardiogram.

Acceleration NON′ Wave.—A very low N′ wave (Fig. 5) is seen in some normal subjects and no relationship to any cardiovascular event has thus far been observed. The NON′ segment of the acceleration ballistocardiogram occurs during cardiac diastasis and the configuration of the acceleration ballistocardiogram appears to conform if the assumption is made that the rapid inflow phase represented in the ballistocardiogram is due to the recoil forces.

Velocity $\dot{N}\dot{O}\dot{N}'$ Wave.—The velocity $\dot{N}\dot{O}\dot{N}'$ segment shows a very gradual positive slope toward the baseline with a very indistinct $\dot{N}'$ wave.

Displacement NON′ Wave.—During this phase of the cardiac cycle there is a very gradual negative slope toward the baseline and the $\dot{N}'$ wave is never registered.

CONCLUSIONS

1. Ballistocardiograms which are registered with the technique used in this study are completely free of parasitic body oscillations. The mechanism of the production of these parasitic body oscillations has been discussed. When parasitic body oscillations are present, the true ballistocardiogram is masked.

2. When acceleration, velocity, and displacement ballistocardiograms are simultaneously registered with other cardiovascular events, as has been done in this study, a finite relationship is consistently present between the ballistic complexes and the events in the cardiovascular cycle.

3. The ballistocardiograms consistently show clinically negligible temporal distortion in relation to the other cardiovascular events. It should be emphasized that this relationship holds true only when the minimal performance criteria discussed in Parts I[2] and II[3] of this paper are strictly adhered to. If corresponding dynamic performance characteristics can be attained by means other than those described in Part II[3] of this paper, as with a bed floated in mercury,[6] or possibly other types of suspensions, comparable results should theoretically be obtained.

4. The various cardiobàllistic complexes are described and their temporal positioning in the cardiovascular cycle is given.

5. It should be clearly understood that even if a certain ballistic complex consistently registers simultaneously with another cardiovascular event, such as, for example, the opening or closure of the valves of the heart, the actual body movement at that instant of time may not be primarily due to the forces set up by the valvular activity. A more reasonable concept would be that forces of much greater magnitude may be created at the same instant of time from related hemodynamic activity.

6. Data have been given which permit the calculation of the forces which move the body in the head-foot direction. Even though these forces may be expressed in exact numbers, these values must be used with caution. Although we may accurately measure these forces, we must keep in mind that these forces have most likely been modified by the transmissional characteristics of the media

between the source and the skeletal structure. Since we do not know how to evaluate the transmissional losses that may be present nor how they may vary from subject to subject, we are not justified in expressing forces at the source in exact numbers.

7. Cardiac output measurements, if made with the ballistocardiographic technique, are dependent upon force evaluation at the source. Until we know and can express the forces at the source in exact numbers, the utility of the ballistocardiograph is of limited value in such applications except for gross relative observations in a subject, as for example, during drug therapy. When noting gross changes in cardiac output, the relationship of the spatial force vector and its resultant effects along the head-foot axis also should be kept in mind. If the spatial vector position should conceivably change without a change in magnitude, the projected effects along the head-foot axis may produce an erroneous concept in relation to cardiac output.

8. In spite of the fact that the forces which move the body may not be the same as at the source, the measurement of the forces which move the body expressed in exact numbers may have value in clinical studies. The probable utility of such measurements has been observed in the study of the abnormal ballistocardiogram. However, until more is known about the force ballistocardiogram in normal and abnormal conditions, it would seem advisable to evaluate the magnitude of the forces which move the body. Similar measurements should be made in the velocity and displacement ballistocardiograms.

9. The most valuable ballistocardiographic information, because it is precise and can be expressed in exact numbers, is the duration of a complex, its relationship to the cardiovascular cycle, the absence or presence of complexes, and the configuration. It has been observed that in normal subjects a definite repeatable pattern exists which does not vary appreciably with age in the adult. In the presence of cardiovascular abnormality, some of the ballistic complexes may undergo considerable change as compared with the normal.

10. Due to the nature of the instrumentation, acceleration ballistocardiograms can always be registered during respiration. In about 10 per cent of normal subjects, displacement and velocity ballistocardiograms may be registered during quiet breathing. The velocity ballistocardiogram is less susceptible to respiration weave than is the displacement ballistocardiogram.

11. Since using the technique described in this paper, the author has for the first time been able consistently to register repeatable ballistocardiographic patterns on normal subjects. A more accurate evaluation of the component complexes, which can be expressed in exact numbers, is possible. With such data, and an understanding of the basic theory and the inherent limitations that are present in the art, a better evaluation of ballistocardiography as a clinical tool does seem possible.

I wish to express my sincere appreciation to Dr. Howard B. Sprague for his help and guidance in this investigation. This study is being continued in collaboration with Drs. Howard B. Sprague and Maurice McGregor in the Cardiac Department, Massachusetts General Hospital, Boston, with particular emphasis on the evaluation of the ballistocardiograms in normal and abnormal conditions.

I gratefully acknowledge the suggestions of Dr. Samuel A. Talbot of the Johns Hopkins Hospital in the construction of the composite sketch (Part III, Fig. 5), particularly with reference to the nomenclature used in the velocity ballistocardiogram, and I am grateful to Drs. W. R. Scarborough and F. W. Davis, Jr., of the Johns Hopkins Hospital, Dr. Isaac Starr of the University of Pennsylvania, and to Dr. W. Dock of the State University of New York Medical College for their encouraging comments and review of some of the data.

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THE SPATIAL ATRIAL GRADIENT

MORDECAI A. BERKUN, M.D.,* RUSSELL H. KESSELMAN, M.D.,*
EPHRAIM DONOSO, M.D., AND ARTHUR GRISHMAN, M.D.

NEW YORK, N. Y.

SINCE 1931, when Wilson[1] first advanced the concept of the ventricular gradient, numerous investigators have studied the qualitative and quantitative aspects of this subject. Scant attention has been paid to the atrial counterpart of the ventricular gradient—the atrial gradient.

The spatial atrial gradient is a sum of the P (representing atrial depolarization) and T_P (representing atrial repolarization) vectors. Mathematically, the spatial atrial gradient is the time integral of the spatial vector representing atrial electrical activity. It gives the magnitude and direction of the electrical forces produced by the lack of uniformity in the duration of the excited state in different portions of the atria.

Study of the electrical events of the atrial cycle has been hampered because most of the T_P wave falls within the QRS complex, the S-T segment, and the T wave. Complete atrial electrical systole can only be seen when marked atrioventricular conduction delay or atrioventricular block is present. It has been noted that P and T_P are ordinarily oppositely directed in leads taken from the external surface of the body. Lepeschkin[2] observed that the area under P and T_P appeared approximately equal and he felt that the atrial gradient was close to zero. Ashman[3] commented that there was a definite correlation between the height of the P and the depression of the P-R segment. Gross[4] made similar observations. We[5] have found a linear relationship between the $P + T_P$ duration and the P-P interval and confirmed that the atrial rate determines the $P + T_P$ duration. The Committee on Electrocardiography of the American Heart Association recommends that the reference level for the measurement of the S-T junction should be the P-R segment at the beginning of QRS.

The opportunity to study the spatial atrial gradient came during our recent work on the spatial ventricular gradient. Correction had to be made for the effect of the deflections due to atrial electrical activity on the QRS complex, S-T segment, and T wave.[7] As a result a large number of electrocardiograms with varying degrees of atrioventricular conduction delay were examined and some were found suitable for this report.

From the Cardiographic Laboratory, The Mount Sinai Hospital, New York, N.Y.
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*National Heart Institute Trainee.

MATERIAL AND METHOD

Sixteen electrocardiograms with complete atrioventricular block were used in this study. The records were from the wards and clinics of The Mount Sinai Hospital. Each record was obtained using a three-channel direct-writing Technicon cardiograph and consisted of simultaneous A, B, and C leads.[8] The electrocardiograms were all taken at a paper speed of 50 mm. per second and standardized so that a 1 mv. input gave a 15 mm. upright deflection. The records were projected on a distant wall with an opaque projector producing a magnification of 12.0 diameters. The P and T_P deflections were traced along their upper margins and an isoelectric base line was drawn. The areas above and below the base line were measured twice with a planimeter and the results averaged. The results were converted into Ashman Units (4 microvolt-seconds) and are recorded in Table I.

Several new symbols are defined and will be used in this and future publications. The symbol g is the magnitude of the spatial atrial gradient while g_A, g_B, and g_C are the magnitudes of the projections of the spatial atrial gradient on the A, B, and C axes, respectively.

From the Pythagorean Theorem

$$g = \sqrt{g_A^2 + g_B^2 + g_C^2}.$$

TABLE I. RESULTS

CASE	AGE	SEX	g_A (A.U.)	g_B (A.U.)	g_C (A.U.)	g (A.U.)
1	70	M	0	−0.6	−0.4	0.7
2	55	M	−0.3	−0.1	+0.5	0.6
3	56	M	−0.5	0	+0.6	0.8
4*	7	M	−0.1	0	−0.2	0.2
5*	44	M	+0.1	−0.4	+0.2	0.5
6	52	F	+0.6	0	+0.2	0.6
7*	34	F	+0.1	0	+0.1	0.2
8*	3 mos.	M	0	−0.5	0	0.5
			+0.3	−0.3	−0.4	0.6
9*	28	M	+0.2	0	−0.3	0.4
10	30	M	+0.1	0	+0.2	0.2
11	67	M	0	−0.3	+0.5	0.6
12	73	M	+0.2	−0.3	+0.1	0.4
13*	5	F	−0.2	−0.6	+0.4	0.7
14	64	M	−0.4	−0.3	+0.5	0.7
15	65	F	+0.4	−0.1	+0.3	0.5
$s = \pm$ 0.2 A.U. (standard deviation)					Average	0.5

*Congenital heart disease. All others had arteriosclerotic heart disease.

RESULTS

The magnitude of g varied from 0.2 to 0.8 Ashman Units in sixteen determinations on the records of fifteen cases. One patient, Case 8, had two determinations because his P waves changed in appearance while the electrocardiograms were being recorded. This is illustrated in Fig. 1.

The patients ranged in age from 3 months to 73 years. There were eleven males and four females. Nine patients had arteriosclerotic heart disease while the remaining six had congenital heart disease.

The mean g was 0.5 Ashman Units with a standard deviation of 0.2 Ashman Units. The percentage of error in the determination of g_A, g_B, and g_C is necessarily large because of the small size of the P and T_P deflections. Base-line wander, tracing error, and error in planimetry are of relatively great importance

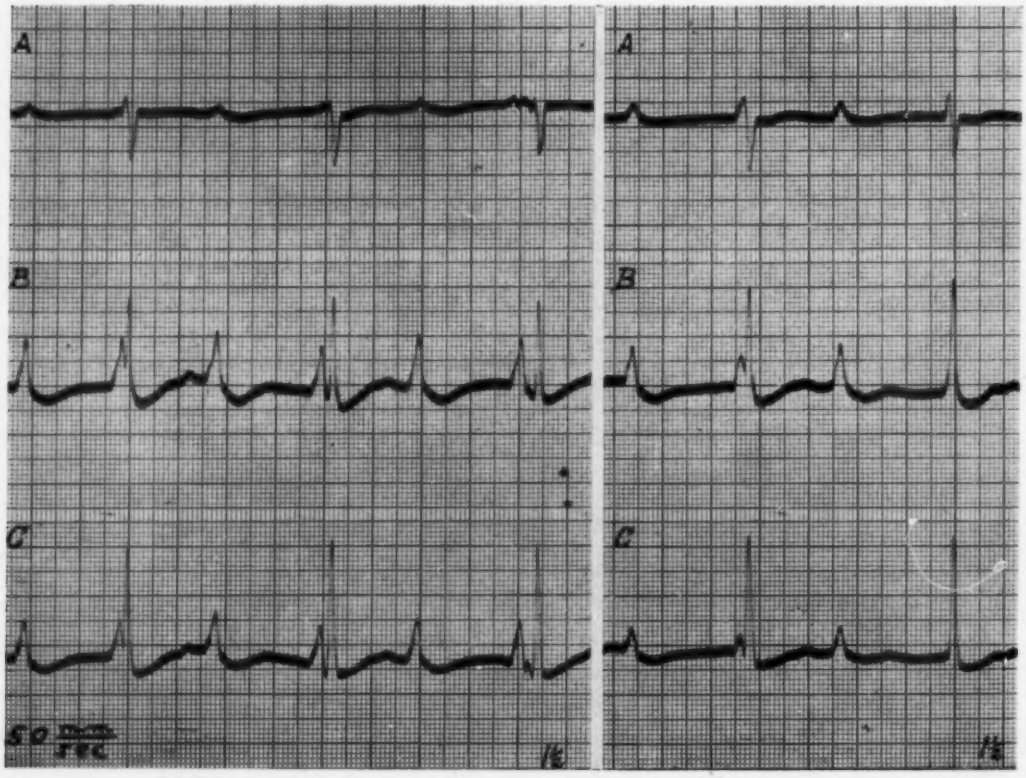

Fig. 1.—Simultaneous *A*, *B*, and *C* leads in a 3-month-old boy with congenital heart disease and complete atrioventricular block. The atrial rate is 150 per minute and the ventricular rate is 71 per minute. These examples are taken from a continuous recording and show the changes in P and T_P that were observed. Because of the changes a separate determination of the spatial atrial gradient was made for each (see results).

when the spatial atrial gradient is determined by this technique. The errors themselves are estimated to be of the order of ± 0.4 Ashman Units. When the spatial ventricular gradient, a much larger quantity, is determined these sources of error are of much less importance.[7]

DISCUSSION

The spatial atrial gradient is a very small vector and may indeed be approximately zero. This indicates that the time course of atrial electrical excitation is close to or perhaps almost identical to the time course of atrial electrical recovery. The area under P is opposite in sign and almost equal to that en-

closed by T_P. A knowledge of the magnitude of the spatial atrial gradient is of the greatest value in the determination of the more important spatial ventricular gradient, particularly when the use of automatic electronic apparatus is contemplated. Since the spatial atrial gradient is close to zero and is a quantity of a small magnitude relative to the spatial ventricular gradient, the time integration for the ventricular gradient can begin at any isoelectric point preceding the P wave and end at any isoelectric point following the T wave (neglecting the U wave). The effect of atrial electrical activity effectively cancels itself and the result obtained is only from ventricular electrical activity. Complicated corrections for the effects of the T_P wave on the ventricular complexes need no longer be made.[7] Another simplification is also possible. Theoretically, the time integration can begin and end at the corresponding point in the electrocardiographic deflections of any two adjacent cycles.

The discovery that the spatial gradient is a vector quantity of relatively small magnitude (almost zero) greatly facilitates the determination of the spatial ventricular gradient. With the use of the proper electronic circuitry a large field of quantitative electrocardiography can be opened for exploration.

CONCLUSIONS

1. The spatial atrial gradient is an electrocardiographic measurement defined in a manner similar to the spatial ventricular gradient.
2. The spatial atrial gradient may be determined from the A, B, and C leads in cases of atrioventricular conduction delay or block.
3. The magnitude of the spatial atrial gradient is relatively small in comparison with the magnitude of the spatial ventricular gradient and may actually approximate zero.
4. The spatial ventricular gradient may be determined, without significant error, by methods which add the spatial atrial gradient to the spatial ventricular gradient.

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THE T WAVE IN BUNDLE BRANCH SYSTEM BLOCK: THE SIGNIFICANCE OF THE ANGLE FORMED BY THE TERMINAL PORTION OF QRS AND THE MEAN T VECTOR

IRWIN HOFFMAN, M.D., AND JEROME A. SCHACK, M.D.

NEW YORK, N. Y.

THE T wave deflections in bundle branch system block have long been considered as "secondary" to the depolarization (QRS) abnormality, and therefore not useful in evaluating the repolarization properties of the myocardium. Grant,[1] as well as Hurst and Woodson[2] have pointed out that although the spatial QRS-T angle in bundle branch system block approaches 180 degrees, the ventricular gradient can be used to judge the repolarization ability of the myocardium.

Calculation of the spatial ventricular gradient can be performed in bundle branch system block; however, special leads as well as considerable mathematics are necessary. The QRS-T angle itself may be difficult to determine, particularly in right branch system block, due to the biphasic nature of the QRS complexes and the subsequent difficulty in plotting a direction for "mean" QRS. We have observed that the last portion of the QRS complex (hereafter referred to as FO4), which is easy to plot spatially, generally makes a very wide angle with the mean T vector in most instances of bundle branch system block. In some instances of block, this angle has been found to be narrow. We have come to regard this narrow FO4-T angle as indicative of severe myocardial disease.

MATERIALS AND METHODS

Technically satisfactory electrocardiograms with QRS duration of 0.12 second or greater were selected at random from the files. In each instance, the terminal 0.04 second of the QRS (FO4), and the mean T vector, were plotted spatially using the method of Grant. The angles between these vectors (FO4-T) were determined using plastic models and protractors. In all, 126 tracings were studied, representing sixty-eight right branch system blocks, forty-eight left branch system blocks, and ten unclassifiable by conventional criteria.

RESULTS

Generally, in right bundle branch system block, FO4 was directed anteriorly and to the right, with T posteriorly and to the left (Fig. 1), resulting in a wide FO4-T angle. In left bundle branch system block FO4 was directed posteriorly

From the Department of Medicine and the Electrocardiographic Laboratory, Beth Israel Hospital, New York City, N. Y.

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and to the left, with T anteriorly and to the right (Fig. 2), again resulting in a wide FO4-T angle.

In the 126 electrocardiograms subjected to analysis, FO4-T in 58 per cent was between 50 and 180 degrees, in 18 per cent between 120 and 150 degrees, in 12 per cent between 90 and 120 degrees, and less than 90 degrees in 12 per cent. Thus, in over 75 per cent of the cases studied, FO4-T exceeded 120 degrees.

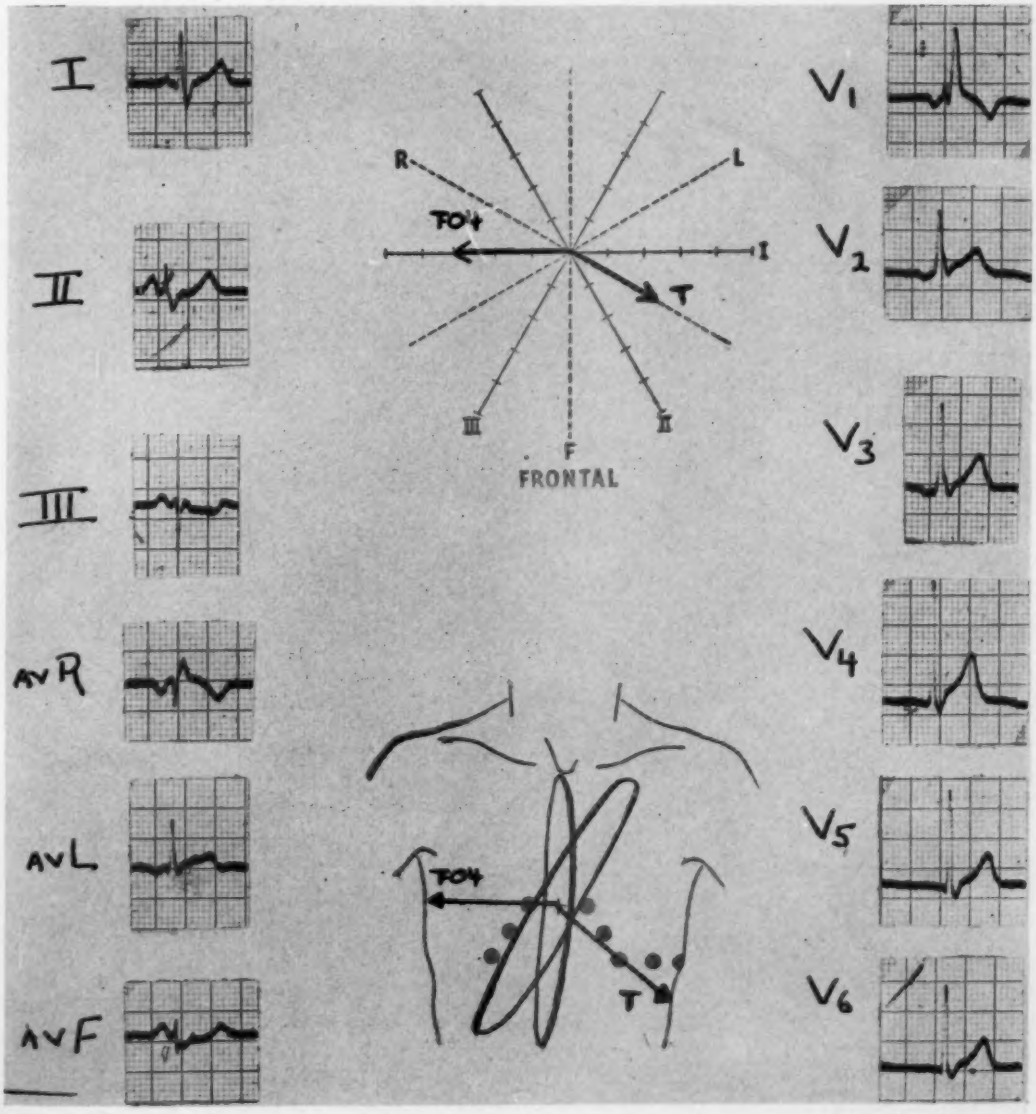

Fig. 1.—Right bundle branch system block. FO4 rightward and anterior, T intermediate and posterior. The FO4-T angle is wide.

Special attention was paid to eleven instances in which the FO4-T angle was less than 110 degrees. In each of these, without exception, review of clinical records revealed that the patient suffered from organic heart disease of severe degree. Seven of the individuals had succumbed shortly after the electro-

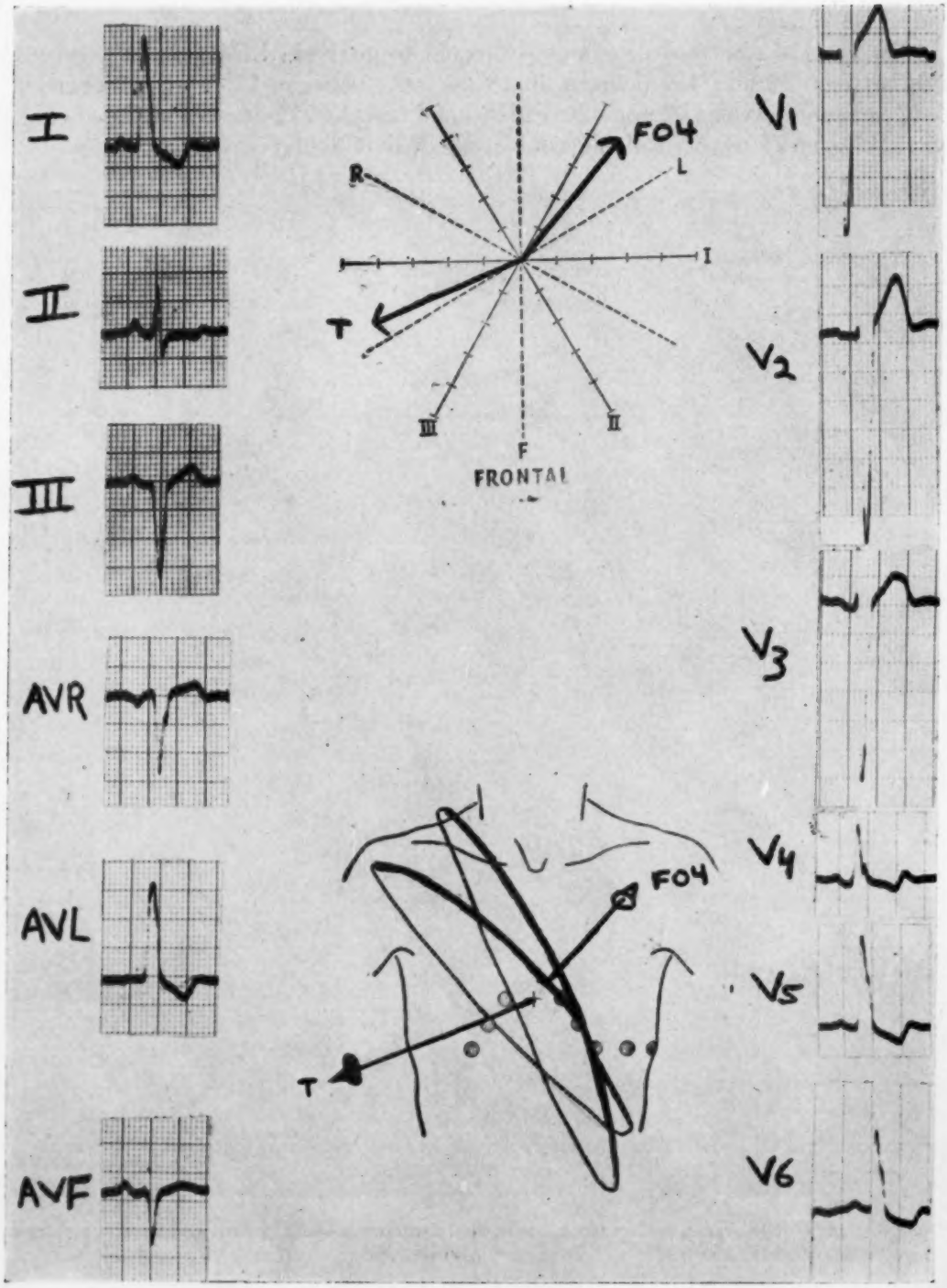

Fig. 2.—Left bundle branch system block. FO4 leftward and posterior, T rightward and anterior. The FO4-T angle is wide.

cardiogram under study had been obtained. The anatomic diagnoses included two cases of long standing multivalvular rheumatic heart disease with diffuse chamber enlargement, four instances of multiple myocardial infarction, and one case of massive recent myocardial infarction.

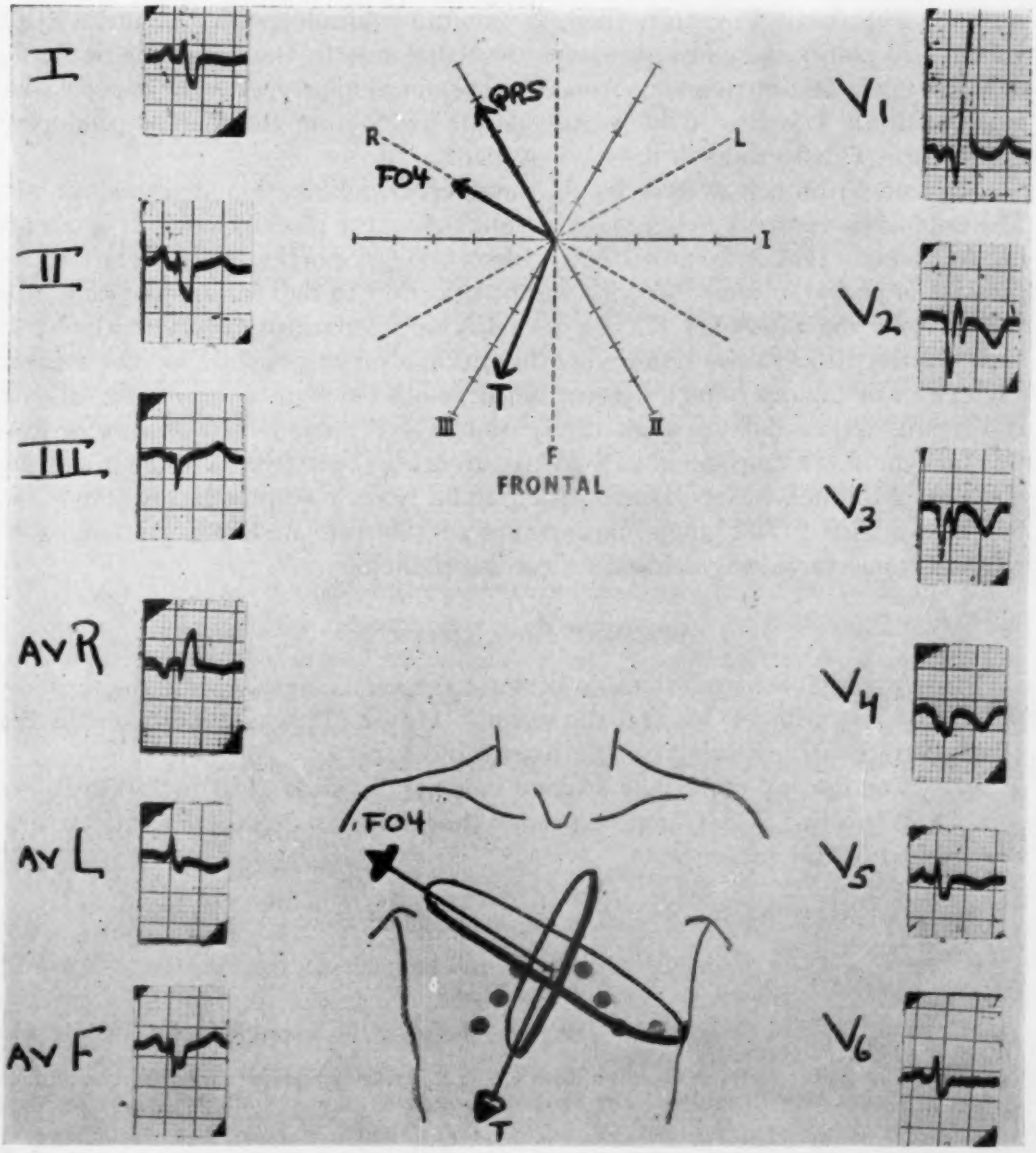

Fig. 3.—Tracing from a 47-year-old man with myocardial infarction. The QRS changes indicate right bundle branch block and septal infarction. The FO4-T angle is narrow (100 degrees).

In contrast with usual relationship between FO4 and T, Fig. 3 illustrates the findings in a patient with severe heart disease. This individual, a 47-year-old white man, was hospitalized for typical myocardial infarction. During his illness a second episode of infarction occurred, during which right bundle branch system block appeared. The spatial FO4-T angle is 100 degrees, and the QRS deflections indicate myocardial infarction as well as conduction defect.

DISCUSSION

The upright T wave in left ventricular epicardial leads of the normal heart is believed due to subendocardial delay in repolarization. Thus, the pathway for repolarization is from epicardium to endocardium, opposite that of depolarization. The mean T vector, then, is generally parallel with the mean QRS vector, and points away from the subendocardial muscle, the site of the normally delayed repolarization process. Areas of ischemia, similarly, are slow to repolarize and the mean T vector in such cases points away from these areas producing appropriate T deflections in the various leads.

In bundle branch system block, however, depolarization is asynchronous. The unblocked ventricle may repolarize long before the blocked side. It is tempting to theorize that in bundle branch block the last portion of the heart to repolarize is probably identical with the last portion to depolarize, and that this accounts for the wide FO4-T angle seen so characteristically in the majority of such electrocardiograms. However, the mechanism responsbile for the narrow angle seen in bundle branch system block associated with severe heart disease is obscure. Nevertheless, when the spatial FO4-T angle is 110 degrees or less, this fact should be considered as evidence favoring the diagnosis of organic heart disease. Although heart disease with bundle branch system block may often manifest a wide FO4-T angle, no instance of a narrow angle has yet been seen without some convincing evidence of cardiac pathology.

SUMMARY AND CONCLUSIONS

1. A study of the relationship between the vector representing the terminal 0.04 second of QRS (FO4) and the mean T vector (T) was undertaken in 126 electrocardiograms showing bundle branch block.
2. The spatial angle thus studied is generally wide (120 to 180 degrees).
3. When this FO4-T angle is narrow (less than 110 degrees) organic cardiac disease is probably present.

We wish to thank Dr. Harry Vesell for his advice and criticism.

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THE TsÊ LOOP IN MYOCARDIAL LESIONS

Preliminary Report

H. Karni, M.D.*

Stockholm, Sweden

IN NORMAL vectorcardiograms (VCG) the TsÊ loop, which is due to recurring resting potentials in the myocardial fibers, usually appears spindle-shaped or elliptic. It is caused by the movable head of the instantaneous vector rapidly changing its magnitude and direction during the repolarization phase of the cardiac cycle. An instantaneous vector is the resultant of manifest repolarization potentials at the actual moment. Its zero point is invariable and in common with that of the PsÊ and QRSsÊ loops. The long axis or maximal instantaneous vector which dominates the shape of the loop is concordant with the long axis of the PsÊ and QRSsÊ loops. The TsÊ loop is normally closed owing to the unchanged zero point.

The resting state does not return simultaneously to all parts of the myocardium. This normal inhomogeneity depends upon the variable thickness of the heart muscle wall and its peristaltic-like movement during systole. The TsÊ loop is believed to be produced by the repolarization potentials from the thickest part of the myocardium where the systolic contraction reaches its maximum.[1] The myocardial area with the maximal intramural pressure during systole is assumed to be the cause of the manifest T vectors.[2] Vectors from the entire myocardium participate in the repolarization, but normally not all components are manifest.

The literature today is scanty as to the nature of the spatial TsÊ loop in myocardial lesions. However, there are a number of interesting phenomena of both practical and theoretical interest. The purpose of this article is to present a preliminary report of investigations on the character of the TsÊ loop in myocardial lesions as well as the theoretical considerations arising therefrom. The phenomena presented below are not dependent on the projection method employed.

APPARATUS AND METHODS

A four-channel, double tube cathode-ray oscilloscope was used. Its technical data have been presented earlier.[3]

To produce VCG projections, leads recommended by Goldberger[4] were used. The frontal plane projection was composed of Leads I and aV_F, sagittal plane projection of Leads V_1 and aV_F, and, lastly, the components of the hori-

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*Present address: Astrakang. 4, Stockholm-Vallingly, Sweden.

zontal plane were Leads V_1 and I. When necessary, the spatial angles of the axes of different loops were determined by means of a coordinate system.[3] Some controls were carried out by the method introduced by Grishman and associates.[5]

MATERIAL

This report is based upon seventy-one cases. Myocardial conditions which have been investigated hitherto with respect to the new considerations of the shape and size of the TsÊ loop are grouped clinically as follows:

DIAGNOSIS	NUMBER OF CASES
Cardiosclerosis and angina pectoris	17
Cardiosclerosis and cardiac decompensation	1
Cardiosclerosis and myocardial infarction	3
Arterial hypertension	1
Congenital organic heart defects	2
Organic mitral defect	1
Trauma cordis	1
Hypercholesterinemia	14
Gastric ulcer (hypopotassemia)	1
Pernicious anemia	1
Total	41 cases

Five representative cases are selected in order to exemplify in this paper the new method of diagnosis.

The results of the investigation of hypercholesterinemia cases will be reported separately.

I. *The TsÊ Loop in Normal Cases.*—The normal series comprises thirty healthy physicians, students, nurses, and hospital workers between the ages of 22 and 69 years.[3] They all showed a narrow TsÊ loop with a distinct long axis. Often it was not even possible to distinguish between the efferent and afferent limbs. The afferent limb returned in all these normal subjects to the zero point. These results are in accordance with those obtained by other authors in normal subjects.

II. *The Pathologic TsÊ Loop.*—

A. *Disintegration of the resultant T vector:* Any myocardial lesion producing pathologic currents may be related to two basic factors: (1) failure or destruction of the myocardial unit and (2) disturbance of the equilibrium between extra- and intracellular ions.

In the following, local death of myocardial fibers and its influence upon the vector field of the repolarization potentials, as seen from the TsÊ loop, will be exemplified in two cases of myocardial lesions.

CASE 1.—(Medical Department I, University Hospital, Gothenburg No. 3004/55.) A 59-year-old man, who had his first episode of myocardial infarction in August, 1953, was admitted for the fourth time Oct. 5, 1955, on suspicion of a new myocardial infarction. Electrocardiographic diagnosis on the day of admission confirmed the suspicion.

Results.—The first vectorcardiographic examination was performed on October 18, when the electrocardiographic tracing already showed considerable regression of the myocardial process.

On the sagittal (S) and horizontal (H) planes the projection of the spatial TsÊ loop was elliptical. There were two long axes, one directed forward and the other backward. The last one concorded with the long axis of the QRSsÊ loop.

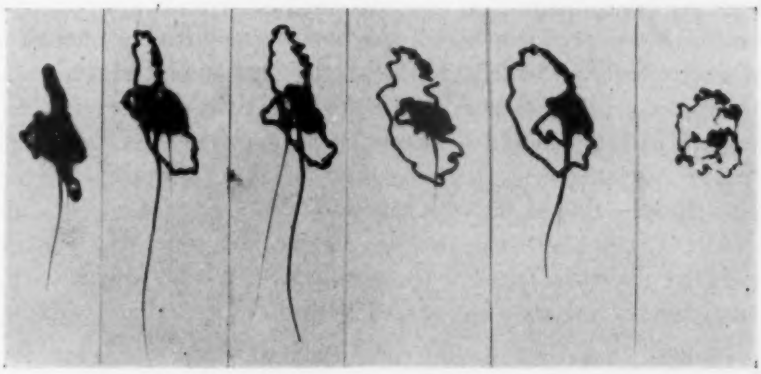

Fig. 1.—Progressive diminution of the TsÊ loop during healing of a myocardial infarction. From the top downward: Sagittal plane projections recorded on thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, and twentieth days of the illness. The QRSsÊ loop is only partially visible. The TsÊ loop is almost unchanged in shape and spatial localization. As shown in the projection taken on the twentieth day, there are two centers of repolarization after healing of the acute process. Amplification: 1 mv. = 9 cm. on the screen.

Follow-ups, carried out on the thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, and twentieth days of the illness, showed a remarkable diminution in the area of the TsÊ loop on each projection plane during healing of the myocardial process. On the twentieth day there were only two maximal vectors in the TsÊ loop. Observations were made from the projections of the TsÊ loop on the H, S, and F planes. Fig. 1 shows the progressive areal decrease of the TsÊ loop, seen from the sagittal plane projection. To establish that this was not due to a change in the spatial localization of the TsÊ loop, its area was planimetrically measured both from horizontal and sagittal and frontal plane projections. The results were as follows:

DAY OF ILLNESS	H	S	F
13	1 (5)	1.36 (6)	0.55 (4)
17	1 (2)	1.28 (1)	0.40 (2)
18	1 (8)	0.70 (3)	0.24 (7)
20	1 (3)	0.24 (6)	0.20 (6)

The figures in parentheses indicate the number of exposures from which the average area was estimated. The reason why different numbers of exposures were used is that the average planial area of the TsÊ loop was estimated

from all available exposures made at each examination, when this detail of the investigation was not yet planned. On each occasion the area of the TsÊ loop on the frontal and sagittal plane projections was compared with that on the horizontal plane. Due to the narrowness of the TsÊ loop on the frontal plane, estimation of its area presented difficulties. However, there is no doubt that it diminished progressively, as shown by the figures above.

Discussion.—The conclusion that there was a real diminution of the area of the TsÊ loop during healing of the myocardial process seems to be justified. The widening of the TsÊ loop was apparently associated with the myocardial lesion. By destroying myocardial fibers, the lesion eliminated a number of vectors participating in the integration of repolarization potentials. This disturbed the electrical equilibrium of the repolarization. Component vectors, in normal cases not manifest, here seemed to influence the new resultant of vector integrations. These vectors derived from intact parts of the heart muscle. However, the more the process healed the more the components disappeared; i.e., the disintegration of the resultant T vector eventually decreased.

The next case represents a myocardial lesion of traumatic etiology.

CASE 2.—(Medical Department I, University Hospital, Gothenburg No. 2861/55). A 53-year-old man was struck on the chest by an iron pipe. He immediately complained of severe radiating pains in the heart region. The clinical picture resembled that of an acute myocardial infarction. ECG tracing, made on the day of admission (September 22), verified a myocardial injury (Fig. 2, left).

Results.—The first vectorcardiographic examination one day later showed most interesting changes in the sagittal plane projection. Here the TsÊ loop was elliptical. There was total loss of its long axis, substituted by two other maximal vectors, one pointing backward, the other forward.

Seven days later the TsÊ loop on the sagittal plane projection was still widened, though it showed an ellipsoid tendency, with its long axis increasingly concordant with that of the QRSsÊ loop. This development continued, and one month after admission, the TsÊ loop of the S plane projection was narrow, the long axis being predominant and concording with that of QRSsÊ, forming an angle (dA) of 30 to 40 degrees.

Discussion.—The progressively diminishing effect of normally nonmanifest vector components from the intact parts of the heart muscle resulted in the development of the TsÊ loop from an ellipsoid figure with two maximal vectors pointing in opposite directions to a fusiform figure with its maximal vector concordant with that of the QRSsÊ loop. Pathologic components were eventually suppressed by vectors from the healed part of the heart muscle.

In this case, too, planial recording of repolarization potentials, compared with the conventional ECG, was a sensitive indicator of the balance between pathologic component vectors and those normally participating in the formation of the TsÊ loop. Electrocardiograms, unchanged since October 3 (Fig. 2, right), showed less variability.

These cases show that when a myocardial fiber membrane fails to be recharged, a vector entity will be lost from the instantaneous vector integration of the repolarization potentials. This does not influence the integration by a simple subtraction alone; it seems to affect the total vector field, composed by

the movable head of the instantaneous vector. New-formed resultants, integrated by hitherto nonmanifest components from intact parts of the heart muscle, may now dominate the formation of the TsÊ loop and distort it. The long axis of the TsÊ loop, which determines its shape, may totally disappear. The phenomenon, here called disintegration of the T vector, is the opposite to the progressive vectorial summation of the heart muscle potentials in normal action.

Both examples above were taken from a series of eleven cases with verified myocardial lesions. In all of these cases the theory of the disintegration of the resultant T vector was found to be applicable with respect to the diagnosis and

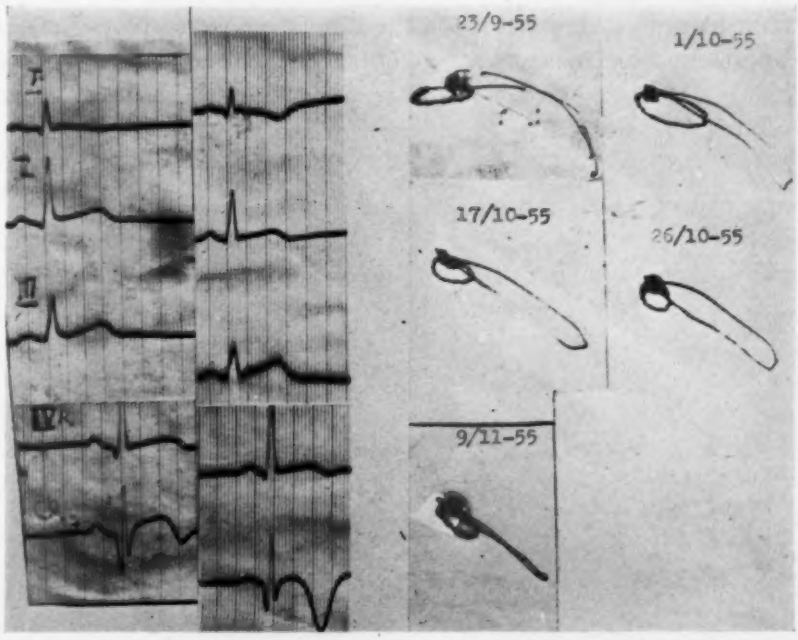

Fig. 2.—Development of a single repolarization center during the healing of a myocardial lesion. The TsÊ loop, at the outset almost ellipsoid, with its long axis now the maximal vector of the TsÊ loop, is concordant with the long axis of the QRSsÊ loop. The disturbed equilibrium has a constant influence on the TsÊ loop, which changes its shape and spatial localization. The TsÊ loop on September 23 and on November 9 is of similar shape and size. However, there are two maximal vectors on September 23. One of them disappeared during healing. The F and H plane projections were normal. Amplification 1 mv. = 3 cm. on the screen. Electrocardiograms showed no changes from October 3 to November 11 (right). ECG on the day of admission (left).

evaluation of the dynamics of the process. Changes of the TsÊ loop in these cases were fully consistent with the experience of myocardial lesions experimentally produced by thallium in dogs.[3] These studies constitute the basis of the present investigations.

The physical nature of the disintegration of the resultant T vectors may be clarified by a simple vectorial synthesis of two perpendicular alternating currents of 50 c.p.s. Morphologically the normal T wave and the sinus wave of alternating currents are approximately alike, though the origin of the T wave is naturally quite different. Vectorial summation of two perpendicular T waves on the screen of the cathode-ray tube and that of two alternating currents conform, of course, to the same vector laws. When two alternating currents of

equal amplitude are vectorially summarized on the screen of the cathode-ray tube (or in the XY-coordinate system), the resultant of these two waves will be a straight line forming an angle of 45 degrees with the horizontal and vertical axes. Its length will be the amplitude of the sinus wave multiplied by $\sqrt{2}$. When the sinus waves show displacement of phase with respect to each other, the resultant will be an ellipsoid figure whose short axis will progressively increase with mounting displacement of the phase. When the latter is 5 milliseconds the short axis will amount to one-half of the long axis (Fig. 3). A change in amplitude of one or both of the sinus waves will result in a directional change of the long axis.

The physical phenomenon fundamentally responsible for the widening of the TsÊ loop in myocardial lesions is the displacement of phase in one or both of the component electrocardiograms.

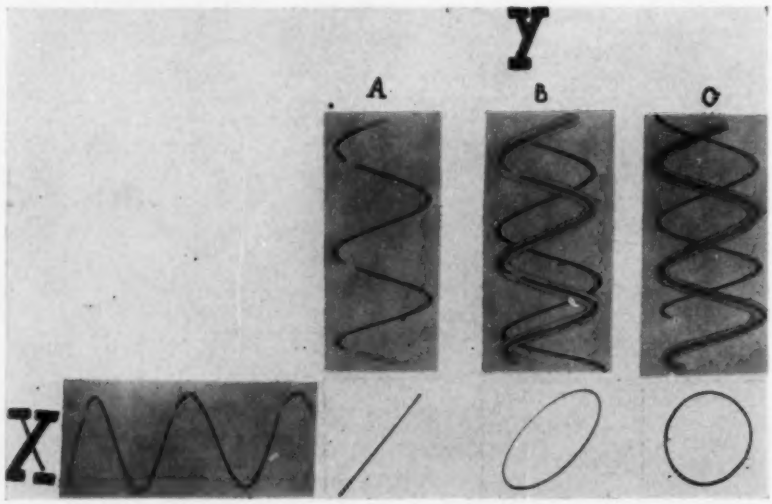

Fig. 3.—Showing vectorial summation in XY-coordinate system of two alternating current waves of sinus type and equal amplitude: each wave 20 milliseconds. *A*, Two waves with no displacement of phase. The summation figure is a straight line forming an angle of 45 degrees with both axes. Its length is the amplitude of the sinus waves times $\sqrt{2}$. *B*, Displacement in phase of the vertical sinus wave of 5 milliseconds, producing an ellipsoid summation figure whose short axis is one-half its long axis. *C*, Displacement in phase of the vertical sinus wave of 10 milliseconds as compared with *A*, resulting in wide summation figure.

Usually it is a question of small intervals of time. A displacement in phase of 2.5 milliseconds will produce an increase of the short axis to one-fourth of the long axis of the ellipsoid figure. In an ordinary electrocardiogram, however, 0.02 second represents the smallest measurable time unit. Further difficulties in verifying disintegration of the resultant T vectors from T waves in various electrocardiographic leads lie in the frequently shifting amplitude of those waves. When there is a major displacement of phase, it can be recognized electrocardiographically as a retardation of homonymous points.

It should be emphasized that the areal change in the TsÊ loop during progression or during healing of a myocardial lesion is not due to changes of the electrode positions from one examination to another. The following facts support this view: (1) Follow-up study may reveal a considerable change in the TsÊ loop, though no demonstrable changes in the component electrocardi-

ograms; and (2) The changes in the TsÊ loop are detectable, though not to the same degree, when the cube system of Grishman and associates is employed.

B. *Potential of Injury.*—Closer analysis of the spatial TsÊ loop helps to elucidate the potential of injury. This produces a very common distortion of the TsÊ loop quite different in nature from that in disintegration of the T vector. It is not due to vectors substituting those of destroyed myocardial fibers, but is caused by potentials from fibers with disturbed activity. Insufficient production of potential in this case is caused by disturbances in the balance between extra- and intracellular electrolytes secondary to the changed structure of myocardial fibers.

To exemplify the influence of a disturbed charging capacity of the injured myocardial fiber membrane, the effect of potassium ion deficiency in normal heart muscle will be shown in the following case.

CASE 3.—(Surgical Department, University Hospital, Gothenburg, No. 5319/55.) A 50-year-old man, suffering from gastric ulcer, was admitted for attacks of vomiting with dehydration and hypopotassemia. When first examined vectorcardiographically, his serum potassium level was 14 mg. per cent. Electrocardiograms showed positive afterpotential.[6]

Results.—The principal vectorcardiographic finding was an open TsÊ loop in the F and S plane projections. The TsÊ loop was fairly small and almost triangular. There was a deficit of 0.1 mv., indicating a residual potential in the myocardium after the depolarization process had terminated, when normally there should have been no potential difference at all. An additional finding was the poorly differentiated long axis of the TsÊ loop.

The areal proportion between the TsÊ and QRSsÊ loops in the F, S, and H planes diminished markedly when normopotassemia returned. The relations were as follows:

	F PLANE	S PLANE	H PLANE
Serum potassium 14 mg. per cent	1:6 (5)	9:113 (3)	1:103 (3)
Serum potassium 20 mg. per cent	12:26 (3)	3:41 (3)	1:5 (3)

The figures in parentheses indicate the number of exposures from which the mean areal value was estimated. The conclusion seems to be justified that the area of the spatial TsÊ loop increases when the electrolyte equilibrium in the heart muscle is normalized (Fig. 4).

Discussion.—The disturbed electrolyte balance associated with hypopotassemia doubtless has a deleterious influence especially on the repolarization of activated myocardial fibers. This is readily understood in view of the well-documented role potassium ions play in the electrical activity of the myocardial fibers.[7] Deficiency of these ions causes a diminished diffusion potential in the heart muscle by preventing adequate charge of membranes. The residual potential difference, before the commencement of repolarization, is probably due to a local minimum or maximum of the potassium concentration in the myocardium, or is related to peculiarities in the uptake of potassium ions in part of the myocardial fibers. Consequently, the residual potential difference in

the myocardium is attributable either to a low uptake or a low concentration of those ions in a part of the myocardial fibers.

When a local structural failure occurs, there will possibly be an insufficient concentration of potassium ions due to the disturbed charging capacity of the membranes in question. This will lead to a local change of the diffusion potential, which may be responsible for the residual potential difference. In the following, this potential, which does not show the same rhythmicity—if any—as the potential variations of the normal heart muscle action, may be called the potential of injury.

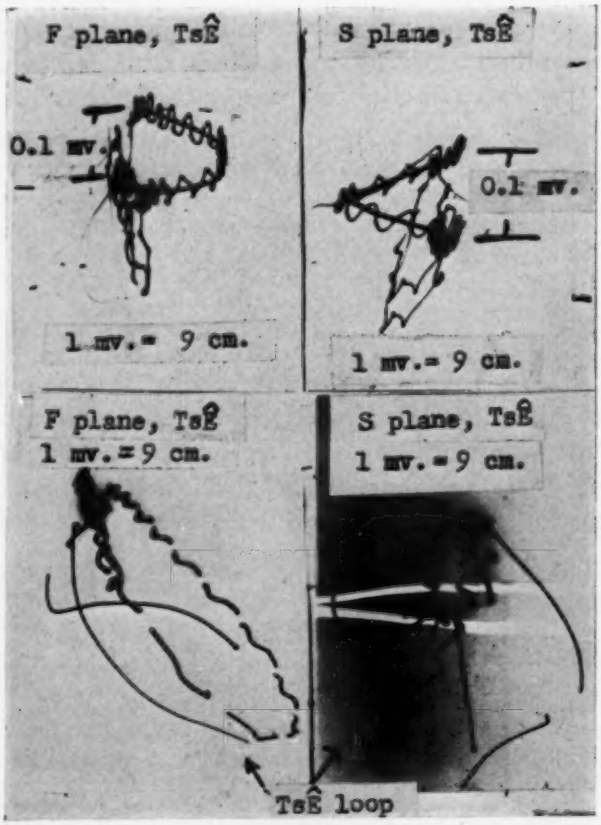

Fig. 4.—Change of the TsÊ loop in the F and S plane projections when serum potassium was 14 mg. per cent (above) and 20 mg. per cent (below). In hypopotassemia it is open at 0.1 mv.; in normopotassemia closed. (The above figures are retouched on account of alternating current disturbances.)

The following cases will illustrate how the potential of injury as observed in the TsÊ loop is applicable to the diagnosis of structural myocardial lesions.

CASE 4.—(Medical Department II, University Hospital, Gothenburg, No. 1176/52.) A 45-year-old housewife, since 1949, had suffered from severe anginal pain radiating from the precordial region toward both arms and the back. When first admitted in 1952, B. P. was 190/95 mm. Hg. During her second stay in the medical department in September, 1955, B. P. was 130/70 mm. Hg. She was cholecystectomized shortly before admission to the medical department. However, the anginal pain was more severe after the operation, and now often occurred in recumbency.

Chest roentgenograms showed general enlargement of the heart. Heart volume was 500 c.c. per square meter body surface.

Results.—The patient underwent vectorcardiographic examination two weeks after admission, when she still had severe attacks of angina pectoris, even at rest and, especially, in recumbency. At this time the ECG showed coronary insufficiency corresponding to the left ventricle. There were no signs of infarction.

The vectorcardiogram yielded more detailed information. The projections taken with maximal amplification showed discordance between the long axis of the QRSsÊ loop and a part of the T vectors.

The TsÊ loop was circular. This could be seen best from the horizontal plane projection (Fig. 5). There was also a residual potential difference which left the TsÊ loop open.

Discussion.—Normally nonmanifest component vectors were here responsible for the shape of the TsÊ loop. Loss of elementary vectors from the integrations was apparently in direct proportion to the pathologic process causing death of myocardial fibers, whereas the potential of injury was obviously referable to structural changes in part of the myocardial fibers. The electrical activity of those fibers was disturbed, causing local changes in diffusion potential. An electrolyte disturbance as the primary cause of the potential of injury could be excluded in this case.

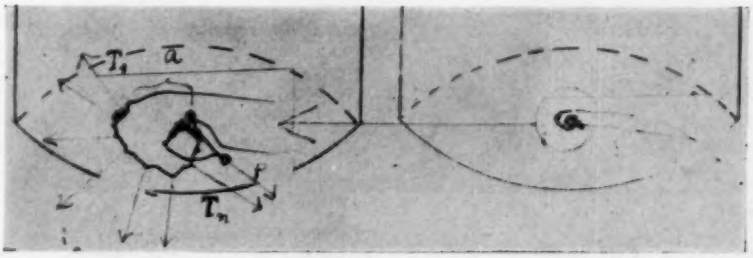

Fig. 5.—Right, Horizontal plane projection in Case 4. Amplification 1 mv. = 3 cm. on the screen. Left, TsÊ loop taken separately with an amplification of 1 mv. = 9 cm. The most marked changes are encountered in the projection in question. The TsÊ loop is open at 0.2 mv. (*a* in the left figure). There is no definite long axis in this loop. Vectors T_1 to T_n indicate the disintegration of the resultant T vector.

Vectorcardiographic examination was performed only once in this case. A follow-up study would have been desirable, but was not possible.

Observations will be made as to the stability of the TsÊ loop. When there is an acute infarction, characteristic instability of the shape and spatial localization of the TsÊ loop may be observed. In suspected cases, therefore, repeated examinations are required at short intervals. If there is a constant potential of injury of major duration, the vector of which has an unchanged direction, it will argue against the existence of a necrotic center in the myocardium. If a constant potential of injury appears together with disintegration of the T vector—as in the present case—two possibilities will have to be taken into account.

1. A necrotic parenchymatous process had developed relatively shortly before. In such case there will not yet be any predominant repolarization center in the heart muscle.

2. Diffuse severe ischemia may cause progressive degeneration of myocardial fibers leading to loss of elementary vectors, which will be substituted continuously by vectors from intact fibers. Hence, vector integrations will show rapid variations. Such instability prevents the repolarization from reaching its normal center. This can be established by the absence of a predominant long axis in the TsÊ loop.

The present case is probably referable to the last-mentioned category.

The following case illustrates the course of myocardial infarction in hypertrophied heart muscle, probably associated with advanced myofibrotic changes, as illuminated vectorcardiographically.

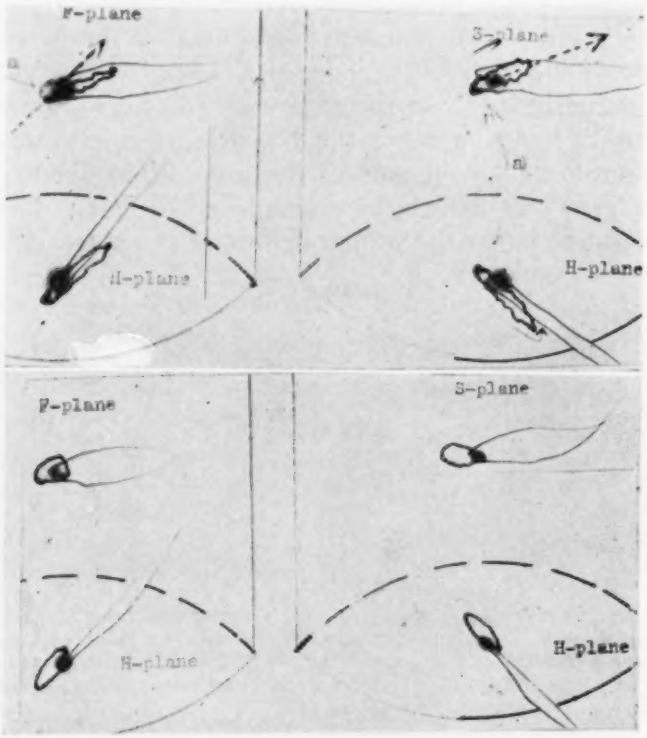

Fig. 6.—*A*, F, H and S, H plane projections in Case 5 one day after the onset of acute myocardial infarction. Amplification 1 mv. = 3 cm. on the screen. There is still a predominant long axis in the TsÊ loop. A potential of injury (*a*) is visible too. Broken-line arrow indicates its direction. The small arrow on the S plane shows the direction of rotation (above). *B*, Same projections four days later. Note the changed shape and spatial localization of the TsÊ loop. There is no definite long axis in this loop any more, nor any considerable potential of injury. The discordance between the long axis of the QRSsÊ and TsÊ loops is increased (below).

CASE 5.—(Medical Department I, University Hospital, Gothenburg, No. 3224/55.) A 59-year-old man was suffering from arterial hypertension, which was established in 1953. Since that year the patient had complained of dizziness. In March, 1955, B. P. was 230/140 mm. Hg. Chest roentgenograms showed enlargement of the left ventricle. On Sept. 25, 1955, the patient was admitted to the Medical Department for myocardial infarction. On the day of admission he had had a sudden attack of severe precordial pain, producing syncope. His skin was cold and moist. B. P. was 200/100 mm. Hg. Electrocardiographic diagnosis—based on demarcation potential in Leads II and III with Q wave in Lead III—verified the clinical suspicions.

Results.—On the second day after admission, the first vectorcardiographic examination was performed.

At this time there was still concordance between the long axes of the QRSsÊ and TsÊ loops. The long axis of the TsÊ loop was still distinct, but instability in the integration of the instantaneous vectors was manifest. The irregular line made by the head of the T vector was caused by the constantly and irregularly changing velocity and potential of the repolarization wave. Due to disturbed balance, there were many equivalent newly formed vector integrations in the myocardium. This, naturally, prevented formation of a vector integration with definite predominance, and increased the duration of the TsÊ loop (Figs. 6 and 7).

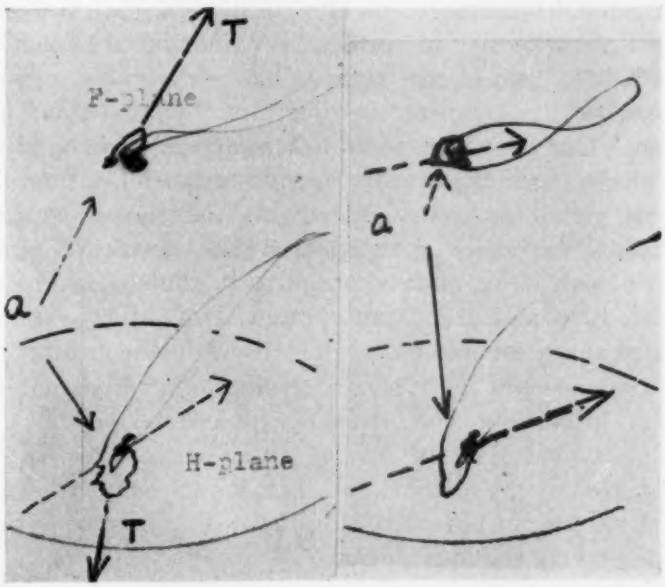

Fig. 7.—Left, Projections on the F and H planes twenty-one days later, when the potential of injury has reappeared (*a*). On this occasion there is also a vague formation of a long axis in the TsÊ loop. Right, F and H plane projections of Case 5, thirty days after the onset of acute myocardial infarction. The TsÊ loop is now even. Its long axis is distinct and the potential of injury (*a*) is pronounced. Amplification 1 mv. = 3 cm. on the screen. The figures are photographically magnified as compared with Fig. 5.

A residual potential difference was detectable. It left the TsÊ loop open 0.1 to 0.2 mv. The line connecting the points where the TsÊ loop commenced and ended was concordant with the long axis of the QRSsÊ loop. Next day the long axis of the TsÊ loop was shorter. Component vectors were becoming prominent. Four days later there was no longer any distinct long axis in the TsÊ loop; the latter was now almost circular. Simultaneously, the spatial localization showed increased instability. This phenomenon, too, could be explained by irregularly changing vector integrations in different parts of the myocardium. Absence of any definitely predominant myocardial part of the repolarization was responsible for this.

The residual potential difference eventually diminished. Its vector changed direction. On the fifth day it was virtually absent. It began to become more marked when long axis returned in the TsÊ loop, and increased with it.

Discussion.—Information obtained from these vectorcardiographic examinations permits conclusions as to the dynamics of the myocardial process. The development of a new long axis in the TsÊ loop and a coincident increase in the potential of injury apparently indicate healing of the acute infarction. The increased discordance between the long axes of the QRSsÊ and TsÊ loops after the acute phase is probably due to increased loss of intact fibers and formation of reparative fibrosis.

Hitherto a residual potential difference has been detected in twenty-three patients with clinically, roentgenologically, or electrocardiographically verified myocardial disease. In six of these it was very marked (0.3 mv. or more). Two of them showed hypertrophy of the right ventricle; two others, hypertrophy of the left ventricle. The former two were incompensated; the latter two had anginal pain. Two of the patients had very severe anginal pain. All of these six showed pathologic electrocardiograms. One of them had had myocardial infarction. One of them with left ventricle hypertrophy simulated, when examined electrocardiographically, a myocardial infarction. This patient was suffering from gallstones, too. Due to the electrocardiographic diagnosis, operative treatment was twice postponed. The vectorcardiograms, checked after an interval of one week, showed stability in the shape and spatial localization of the TsÊ loop and a constant potential of injury. The patient was cholecystectomized and presented no complications during or after the operation.

In three more patients with electrocardiographic findings interpreted as acute myocardial infarction, vectorcardiographic analysis of the TsÊ loop yielded contradictory results. In one of them there was total discordance between the long axes of the QRSsÊ and TsÊ loops, but neither disintegration of the resultant T vector nor potential of injury. Furthermore, the TsÊ showed stability in shape and spatial localization.

Patients 4 and 5 illustrate the similarity of the effect produced by ischemia and by hypopotassemia. However, there are some differences in these two conditions. In the case of hypopotassemia there is a general effect in the entire myocardium, whereas ischemic damage is localized in the main to the left ventricle wall. In the former condition, moreover, the membranes are intact. In the ischemic heart muscle the charging capacity of the membranes is disturbed in some part or parts of the myocardium.

In ischemic damage to the heart muscle, as in the cases reported above, the myocardial fibers will show degenerative changes. Probably the membrane, which has a very delicate structure, will be first affected by the ischemic state, causing metabolic and, later on, structural changes. Injured membranes may not be capable of a normal uptake of potassium ions, and may thus disturb the normal mobility and interchange of extracellular sodium ions and intracellular potassium ions. Consequently, there will be local disturbances of ion concentration and diffusion potential, which will only partially show the same rhythmic variation as the intact part of the heart muscle.

When an intra-arterial process, producing anoxic lesions of the myocardial fibers, progresses, it will lead to obstruction of the artery in question. This will result in necrosis of the ischemic area and partial or total subsidence of

the potential of injury. This may be due to destruction of that part of the myocardium which, prior to the infarction, was most ischemic and probably caused the major part of the potential of injury. Or it may be referable to disturbing factors, such as potassium ions and other autolytic products from the necrotic zone. It has been pointed out that potassium ions in excess cause a demarcation potential.[3,8] At all events, the potential of injury increases when the infarction has healed. This peculiar phenomenon has been encountered by the author in three further cases of myocardial infarction.

Summarizing, the potential of injury is a sensitive indicator of anoxic damage to the membranes. It often appears parallel with the depression of the S-T segment in the conventional ECG, but planial recording affords a greater chance of its detection. Stereometric study of the potential variations during the cardiac cycle also enables the spatial localization of its vector to be determined.

The TsÊ loop of an extrasystole in three cases of heart failure showed potential of injury. This was very marked in one patient who had long been under digitalis therapy. The TsÊ loop of extrasystole in two young persons did not show any residual potential difference. Further investigations of this problem are required.

SUMMARY

A preliminary report on a new method of analyzing the TsÊ loop in myocardial lesions is presented. The analysis is based on two pathologic phenomena: (1) disintegration of the resultant T vector, and (2) the potential of injury.

Analysis of the TsÊ loop in myocardial lesions, based upon the theories of disintegration of the resultant T vector and potential of injury, was found to be serviceable in forty-one cases. Changes in the T vector field are similar in character to those associated with myocardial lesions produced experimentally by thallium in dogs. The potential of injury due to local anoxic damage resembles the residual potential difference in electrolyte disturbances caused by hypopotassemia. Pathologic TsÊ loops are compared with those obtained from thirty normal subjects.

I wish to express my graditudé to Associate Professors L. Werkö, P. Nordquist, and B. Hood for their helpful criticism and great interest during the present investigation.

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THE ELECTROCARDIOGRAPHIC FINDINGS IN PATIENTS UNDERGOING SURGICAL EXPLORATION OF THE MITRAL VALVE

RAYMOND D. PRUITT, M.D., AND JOHN G. ROBINSON, M.D.

ROCHESTER, MINN.

THE major purpose of this account is to report on the relation between the electrocardiographic findings and the morphologic changes in the mitral valve in a series of 147 patients, all of whom underwent surgical exploration of that valve. A secondary end is to present data derived on comparing the electrocardiograms made immediately preoperatively with those recorded several months postoperatively in thirty-four patients undergoing surgical exploration of the mitral valve.

The essential data bearing on the first objective are contained in Table I. In the left-hand column, the morphologic classification is indicated. Distribution of cases under this classification was made solely on the basis of the tactile observations of the surgeon as accomplished at the time of surgical exploration of the mitral valve. These operations were performed by one or the other of two surgeons, Dr. John W. Kirklin or Dr. F. Henry Ellis, Jr., to whom we are indebted for information regarding the nature of the valvular deformity as defined at the time of the commissurotomy. When the surgeon could introduce only the tip of his examining finger into the valvular orifice, the patient was considered to have severe mitral stenosis. Moderate mitral stenosis was said to exist when the examining finger could be passed into the orifice for a distance of approximately 1 cm. Regurgitation was considered to be slight in degree when a weak jet of blood could be felt in the left atrium coming commonly from only a localized region of the valvular orifice.

The electrocardiographic categories given in Table I can be defined most revealingly by reference to Figs. 1 and 2. Electrocardiograms of Type 1 exhibited complete or partial right bundle branch block. Type 2 includes tracings characterized by changes pathognomonic of right ventricular hypertrophy. Types 3 and 4, on the basis of right axis deviation in the standard limb leads and QRS complexes in precordial Lead V_1 of the kind illustrated in Fig. 1, were considered suggestive of right ventricular hypertrophy but not definitive of it. Type 5 consists of a group of electrocardiograms considered to be within the limits of normality as commonly accepted. Type 6 includes tracings in which varying degrees of evidence of left ventricular hypertrophy were present.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn., a part of the Graduate School of the University of Minnesota.

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In division A of Type 6, this evidence consisted only of the presence of an intrinsicoid deflection in Lead V_5 or V_6, or both, the onset of which occurred 0.04 second after the earliest component of the QRS complex. In tracings of Type 6B, the intrinsicoid deflection in leads from the left precordium began about 0.04 second after the onset of the QRS complex as in Type A, but in addition the T waves in the same leads were inverted or were of diphasic character and the RS-T segments were depressed. Type 6C is made up of records in which the intrinsicoid deflection occurred at a time greater than 0.04 second after the

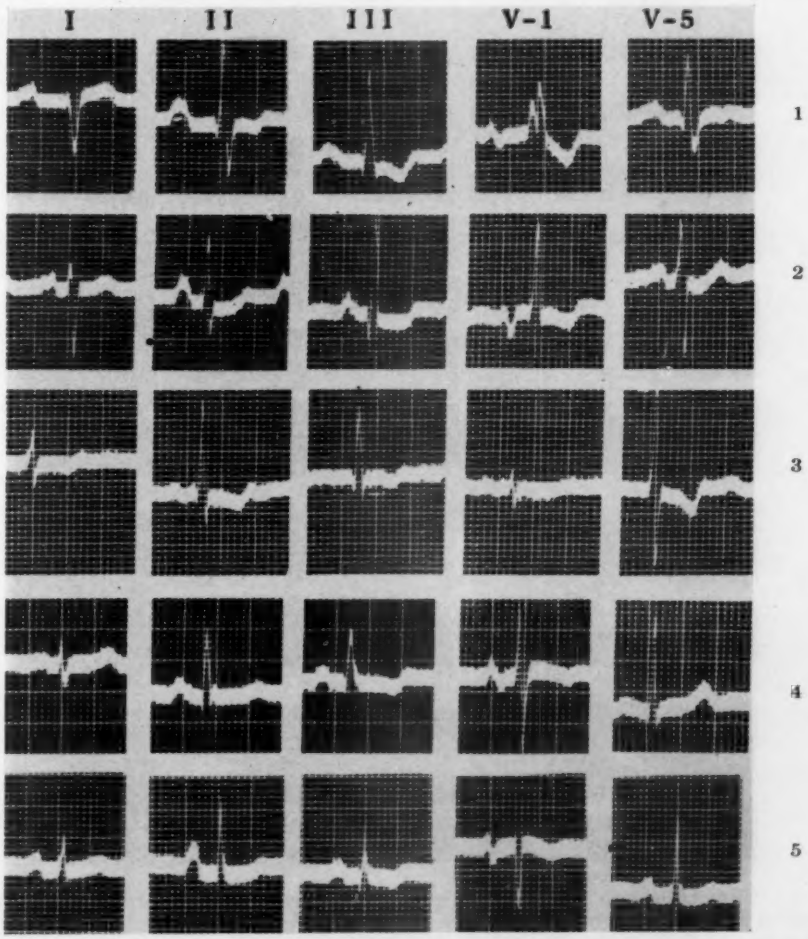

Fig. 1.—Numbers *1* to *5* on the left-hand side of the figure indicate the type of electrocardiogram illustrated in the row of complexes to the right of each number. Type *1* is right bundle branch block. Type *2* is pathognomonic of right ventricular hypertrophy. Types *3* and *4* are suggestive of right ventricular hypertrophy but not definitive of it. Type *5* represents a group of tracings judged to be within the limits of normal.

onset of the QRS complex. In some instances of this type segmental and T-wave changes of the character noted under 6B were present. In others they were not. Type 7 consists of cases in which evidence both of right and of left ventricular hypertrophy was present. The character of the evidence of left ventricular hypertrophy is indicated by the letters A, B, and C which have the

same significance as in Type 6. A single case in which a Wolff-Parkinson-White type of abnormality (short P-R interval with widened QRS complex) existed is listed in the final column; the presence of anomalous atrioventricular excitation precluded definition electrocardiographically of ventricular hypertrophy.

Table II presents a summary of data obtained on comparing, in a series of thirty-four patients, the findings in electrocardiograms made immediately prior to attempted or actual surgical treatment of the diseased mitral valve with tracings made from six to thirty, averaging fourteen, months following the operative procedure. In Fig. 3 are presented examples of the categories

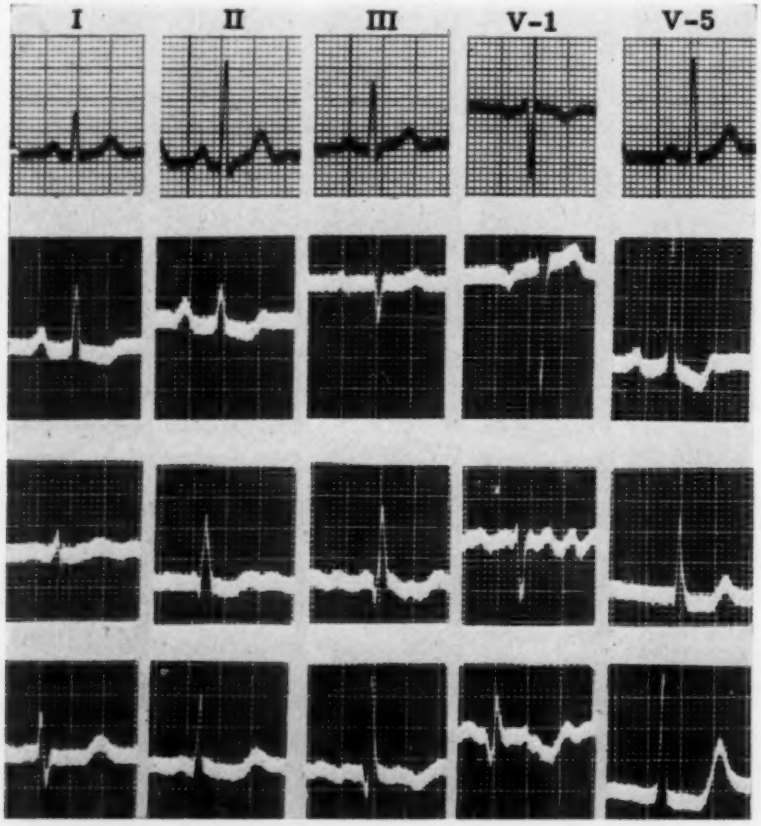

Fig. 2.—Numbering as in Fig. 1. In Type *6A* the only evidence of left ventricular hypertrophy is the occurrence of the intrinsicoid deflection in V_5 at a time 0.04 second after onset of the QRS complex. Type *6B* differs from *6A* only in the presence of inverted or diphasic T waves and depressed RS-T segment in Lead V_5. In Type *6C* the intrinsicoid deflection occurred at a time greater than 0.04 second after the onset of the QRS complex. (At the onset of the QRS interval in Lead V_5 of the illustration chosen for Type *6C* is a small Q deflection not well reproduced in this print.) In Type *7C*, evidence of left ventricular hypertrophy exists, as in *6C*, but there is also evidence of right ventricular hypertrophy in Lead V_1.

of change specified in Table II as "marked reversion toward normal," "moderate reversion toward normal," and "no reversion." The tracing chosen in illustration of "marked reversion" represents the most striking change encountered in the entire series. The record presented as an example of "moderate reversion" represents the slightest degree of change held to be significant

of reversion toward normal. The remaining twelve of the fourteen tracings showing some degree of reversion toward normal lay between the ranges defined by the electrocardiograms reproduced in Series A and Series B of Fig. 3. Series C in Fig. 3 represents that category of tracings in which it was judged that no significant reversion had occurred. It is evident on close review that a slight change toward normal had taken place. The records in Series B and

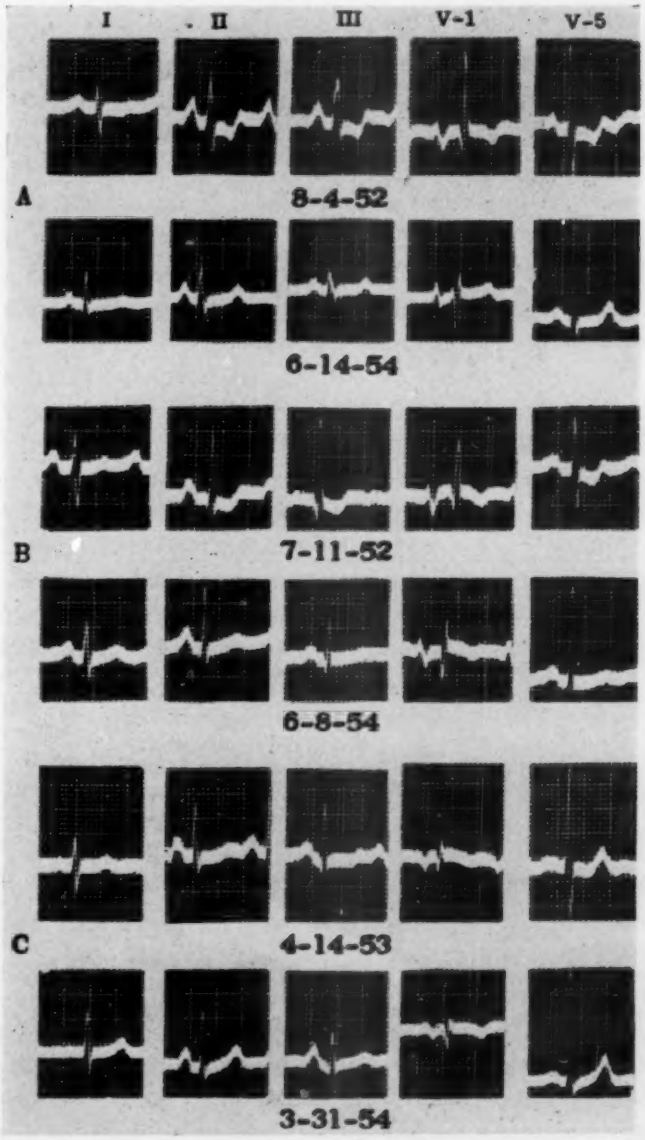

Fig. 3.—Electrocardiograms on three patients, *A*, *B*, and *C*, one set of records for each patient having been made prior to mitral commissurotomy, and a second set six months or more postoperatively. In Patient *A*, marked reversion of the electrocardiogram toward normal had occurred. In Patient *B*, moderate reversion had taken place. In Patient *C*, the degree of reversion was classed as too slight for definite recognition. For additional comment, see text.

Series C of Fig. 3 marked the point of division between cases held to show moderate reversion toward normal and those held to be essentially unchanged.

TABLE I. MORPHOLOGIC AND ELECTROCARDIOGRAPHIC FINDINGS IN 147 CASES OF MITRAL VALVULAR DISEASE

NATURE OF VALVULAR DEFORMITY	ELECTROCARDIOGRAPHIC CATEGORY										TOTAL CASES (ANATOMIC CATEGORIES)
	1	2	3	4	5	6			7	W-P-W* DEFORMITY	
						A	B	C			
Severe mitral stenosis	6	41	10	9	18	6	1		1 (7B)	1	93
Severe mitral stenosis with slight regurgitation	3	10	2	1	2	3	2		2 (1 of 7A; 1 of 7C)		25
Moderate mitral stenosis				1	3	2	1				7
Mitral regurgitation with mild to moderate stenosis		1	1	1	1	4	3	1	4 (3 of 7C; 1 of 7A)		16
Mitral regurgitation without significant stenosis		1	1			1	1	1	1 (7C)		6
Total cases (ECG categories)	9	53	14	12	24	16	8	2	8	1	147

*Wolff-Parkinson-White.

TABLE II. THIRTY-FOUR CASES OF MITRAL VALVULAR DISEASE IN WHICH ELECTROCARDIOGRAMS WERE RECORDED 6 MONTHS OR MORE AFTER SURGICAL EXPLORATION OF THE MITRAL VALVE

VALVULAR DEFORMITY AT TIME OF OPERATION	MARKED REVERSION TOWARD NORMAL	MODERATE REVERSION TOWARD NORMAL	NO REVERSION	TOTAL CASES (ANATOMIC CATEGORIES)
Severe mitral stenosis: no regurgitation	6	5	14	25
Slight regurgitation	2	1	2	5
Moderate mitral stenosis			1	1
Mitral regurgitation: mild to moderate stenosis			2	2
No significant stenosis			1	1
Total cases (ECG categories)	8	6	20	34

COMMENT

A variety of diagnostic measures were applied in selecting, for surgical exploration of the mitral valve, the patients constituting the series on which this study was based. Discretion must be exercised in deriving from such a highly selected series conclusions bearing on the precision with which mitral

stenosis can be distinguished from mitral regurgitation on the basis of the electrocardiographic evidence. It is conceivable, even if unlikely, that the incidence in this series of electrocardiographic findings of left ventricular hypertrophy among patients with uncomplicated mitral stenosis is misleadingly low because some patients with such a lesion were denied surgical exploration inasmuch as their electrocardiograms were indicative of left ventricular hypertrophy. On the other hand, it is far more likely that among patients with mitral regurgitation in this series the incidence of electrocardiographic evidence of right ventricular hypertrophy is higher than it would be in an unselected series of cases of mitral regurgitation simply because the electrocardiographic evidence of right ventricular hypertrophy was interpreted as supporting the presence of a predominantly stenotic lesion and surgical exploration of the mitral valve was recommended and undertaken.

From the data presented in Table I, the following facts may be selected for emphasis and development.

1. Whereas forty-one of ninety-three patients (44 per cent) found to have severe stenosis had electrocardiograms indicative of right ventricular hypertrophy, only two of twenty-two patients (9.1 per cent) with predominant mitral regurgitation had such electrocardiograms.

2. Whereas sixteen of twenty-two patients (72.7 per cent) found to have a predominantly regurgitant mitral lesion had electrocardiograms of Types 6 or 7, only eight of ninety-three (8.6 per cent) patients with severe mitral stenosis had tracings in which evidence suggestive of left hypertrophy was present.

3. Ten of twenty-five patients (40 per cent) with severe mitral stenosis but mild to moderate mitral regurgitation had electrocardiograms indicative of right ventricular hypertrophy, while seven of twenty-five (28 per cent) had tracings of Types 6 or 7. Some suggestion of ambivalency both as to morphologic and electrocardiographic findings existed in this group.

4. Patients with uncomplicated mitral stenosis of moderate degree numbered only seven and among these the electrocardiographic evidence was either of essentially nondefinitive character in respect to ventricular hypertrophy or suggestive of left ventricular hypertrophy.

5. Right bundle branch block, partial or complete, occurred in nine patients, all of whom had either severe mitral stenosis only (six cases) or severe mitral stenosis attended by slight mitral regurgitation (three cases).

In comment on the data presented in Table II, attention may be directed to the fact that in fourteen instances, or slightly less than half of the total series of thirty-four cases, a marked or moderate reversion of the electrocardiogram toward a more normal configuration occurred within a period averaging 14 months for the entire group. An added fact of some significance but not included in the table is that six of the twenty patients whose electrocardiograms remained unchanged postoperatively had essentially normal (Type 5 in Fig. 1) tracings preoperatively, and hence no significant alterations would be anticipated however much improvement might have characterized the patient's clinical course. Of these six patients, four had severe mitral stenosis without regurgitation, one had severe stenosis attended by slight regurgitation, and one

had mild stenosis without regurgitation. Hence, all six instances of normal preoperative tracings were among patients who had a type of valvular deformity that may have been lessened as a consequence of surgical intervention. Of two other patients among the fourteen with severe mitral stenosis in whom no reversion occurred, one had right bundle branch block and the other had incomplete right bundle branch block. Change in an electrocardiographic pattern of this type as a consequence of mitral commissurotomy would not be anticipated. An additional three of this same group of twenty patients had lesions (predominant mitral regurgitation) of a type not subject to amelioration at the time of surgical exploration.

Thus in eleven of the twenty patients whose electrocardiograms showed no reversion toward a more normal pattern during the remote postoperative period, such reversion would not have been anticipated because of the character of the preoperative electrocardiogram or the nature of the valvular lesion. It is of interest that among the remaining nine of these twenty patients, seven experienced excellent operative results, one a fair result, and one was unimproved. Hence absence of reversion in the electrocardiogram cannot be regarded as coincident with a poor operative result.

CONCLUSIONS

1. In a series of ninety-three patients with severe mitral stenosis, the incidence of electrocardiographic evidence indicative of right ventricular hypertrophy was 44 per cent, whereas among twenty-two patients with predominant mitral regurgitation the incidence of such evidence was 9.1 per cent.

2. Electrocardiographic evidence of left ventricular hypertrophy in the presence of uncomplicated severe mitral stenosis occurred in eight of ninety-three patients (8.6 per cent), whereas in the presence of predominant regurgitation such evidence existed in 72.7 per cent of twenty-two cases.

3. Among twenty-five patients with a predominantly stenotic lesion but with associated mild to moderate mitral regurgitation the incidence of evidence indicative of right ventricular hypertrophy was comparable (40 per cent) to that among patients with uncomplicated mitral stenosis. However, in such patients the incidence of electrocardiographic evidence of left ventricular hypertrophy (28 per cent) was somewhat higher than among patients with uncomplicated mitral stenosis.

4. The electrocardiogram may be used rewardingly as an adjunct to other clinical data in establishing the nature of the morphologic changes in acquired disease of the mitral valve. However, deductions concerning morphology derived from the electrocardiographic evidence alone are of a relative and not of an absolute nature.

5. In fourteen instances, or slightly less than half of a series of thirty-four patients, a marked or moderate reversion of the electrocardiogram toward a more normal configuration occurred within a period averaging fourteen months for the entire group. In eleven among the twenty remaining patients in this group of thirty-four, reversion toward a more normal pattern would not have been anticipated because of the character of the electrocardiogram preoperatively or the nature of the valvular lesion.

STUDY BY CATHODE-RAY OSCILLOGRAPHY OF SOME INNOCENT AND PATHOLOGIC CARDIAC MURMURS OF CHILDREN

T. N. HARRIS, M.D., AND HERBERT L. NEEDLEMAN, M.D.*

PHILADELPHIA, PA.

OF THE physical effects due to the circulation which are detectable at the surface of the body, the acoustic phenomena have been the subject of relatively little physical study and analysis. Although Einthoven's adaptation of the string galvanometer to the field of biology 60 years ago resulted in applications to the study of both electrical and acoustic circulatory phenomena, the former has grown into the thoroughly explored field of electrocardiography, whereas the latter has been used primarily for the identification of cardiac murmurs and adventitious sounds and for timing these within the cardiac cycle. (For an extensive bibliography of phonocardiography see Calo)[1]. There may be a number of reasons for this difference between the degree of development of the two fields of investigation. First, the problem of calibration of a string galvanometer is much more formidable in its application to acoustic phenomena than to electrical changes. (The problem of calibration in the recording of heart sounds and murmurs has, in fact, recently been studied by a number of workers.[2-5]) Also, the electrical changes within cardiac tissue are characterized by frequencies, in the main, of a sufficiently low order and narrow range to permit reproduction by a stringed instrument, whereas this is not true of the vibrational frequency of cardiac sounds and murmurs. It may be noted, however, that even in the case of electrocardiography the higher degree of resolution afforded by the cathode-ray oscillograph has made possible the demonstration of higher frequency changes not detected by the string galvanometer.[6-8]

Studies or recordings of circulatory acoustic phenomena of normal subjects or of patients with cardiac disease have recently been undertaken by several workers with instruments which permitted a higher order of resolution or different measurements than does the string galvanometer. Thus Smith and associates[9] used the cathode-ray oscillograph for recording heart sounds and vibrations of normal subjects. Dunn and Rahm[10] also used a cathode-ray oscillograph for recording cardiac sounds and murmurs, in a recording apparatus which involved simultaneous recordings from three different microphones, in

From the Rheumatic Fever Research Laboratory of the Children's Hospital of Philadelphia, the Philadelphia General Hospital, the Children's Seashore House, and the Department of Pediatrics, School of Medicine, University of Pennsylvania.

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*Postdoctorate Fellow of the National Heart Institute, U. S. Public Health Service.

an attempt at localization of the origin of the murmur. Rushmer and associates[11] described an instrument which rectifies and integrates the vibrations which cause heart murmurs, and presents an envelope of the wave of those vibrations. Recently McKusick and associates[12,13] have adapted the sound spectrograph to the study of cardiac murmurs. This instrument, which gives a measure of intensity of vibrational components within given ranges of frequency, has produced very informative graphic representations of various organic cardiac murmurs in the hands of these investigators.

The limited extent to which the acoustic circulatory phenomena have been subjected to physical analysis is particularly unfortunate from the point of view of pediatric cardiology, since the vibrational phenomena which give rise to cardiac murmurs have an order of importance for the pathologic physiology and diagnosis of heart disease in children which may be compared to that of the electrical phenomena reflected by electrocardiographic changes, in the case of heart disease of adults. An understanding of the physical characterization and basis of heart murmurs would be of especial value for pediatric cardiology not only because of the importance of murmurs in the heart disease of children and adolescents but also because of the widespread occurrence of nonpathologic murmurs in these age groups. In a number of studies the rate of occurrence of such nonpathologic murmurs among presumably healthy children has been reported at percentages between 40 and 60,[14-19] and in others somewhat lower rates of incidence have been reported.[20-24] The mechanisms which give rise to these presumably innocent murmurs are not understood, nor can any combination of criteria applicable in physical examination serve to differentiate all organic murmurs from all innocent ones, although a number of useful generalizations have been made on points of difference between these two chief classes of cardiac murmurs.

The present study is one of a series of investigations on some physical characteristics of major groups of organic and innocent cardiac murmurs of children. It has been found useful to consider the nonpathologic murmurs of children in two groups, since these groups appear to embrace at least 95 per cent of all innocent murmurs encountered in the course of these studies. Such grouping of functional murmurs is recognized in other clinics as well. The first of these is the precordial murmur described by Still[25] early in the century as the "twanging-string murmur," and for which the term "precordial vibratory murmur" has been suggested.[26] It is of a buzzing quality, usually not at all harsh, and is generally of maximal intensity in the midprecordium. This murmur decreases in intensity in adolescence and is virtually never heard in adults. The other, the pulmonic-systolic murmur, is of maximal intensity in the pulmonic area. (The name derives from this feature, not from any implied association with the pulmonary valve or artery.) It may be heard with diminishing intensity across the sternum, or downward along the left border of the sternum, or in a diagonal line toward the apex. It can be heard in a range of degrees of roughness or harshness in different subjects. The pulmonic-systolic murmur generally decreases in intensity and in its distance of "radiation" in these directions, so that in those subjects in whom the murmur persists into adult

life is generally of lower intensity and usually confined to the pulmonic area. Murmurs which appear to be of nonpathologic significance are occasionally found outside of these two groups, e.g., with points of maximum intensity to the right of the sternum, or at the lower left border of the sternum, but these are quite rare in comparison with the total of the two categories described above. Within these two categories there are not infrequently instances of overlapping, in which the application of the criteria mentioned above leaves possible differences of judgment as to the category involved. However, in general, the classification of the large majority of all innocent murmurs of childhood into these two groups is quite clear.

In earlier studies of this series wave forms were examined in phonocardiographic tracings of precordial vibratory and pulmonic-systolic murmurs, and of the murmurs of mitral insufficiency. Apparently characteristic differences in wave form were noted among these types of murmurs. Whereas the wave forms seen in the phonocardiograms of murmurs of valvular insufficiency were so complex that no pattern or fundamental frequency could be discerned, those of the precordial "twanging-string" murmur approximated that of a simple, uniform wave of constant frequency, resembling in general a damped sine wave of a frequency in the range of 70 to 130 cycles per second.[26,27] Because the form of the wave was similar to that which would be generated by a structure set into free vibration it was suggested that the designation "precordial vibratory" might be appropriate for this murmur.

The wave form of the pulmonic-systolic murmur showed some similarity to that of the precordial vibratory murmur, in that a simple wave could be discerned, but almost invariably the tracings of this murmur showed some distortion, so that at several points in the wave the regularity of the simple form was lost. However, even with these irregularities relative to an apparently simple wave, the wave form of the pulmonic-systolic murmur was quite clearly different from that of the highly complex form seen in tracings of murmurs of mitral insufficiency.[28]

It was apparent in the course of these studies that substantial limitations were imposed on the fidelity of the graphic representation of these murmurs by the fact that a stringed instrument was employed. It was thought likely that frequencies were encounted in some of the murmurs which were higher than the greatest frequency of vibration possible for the "string" of the galvanometer, and that the reproduction of some of the vibrational components of low amplitude and high frequency might well be above the resolving power of the instrument. Accordingly, an exploration of the wave form of cardiac murmurs of types such as those mentioned above was undertaken by the use of the cathode-ray oscilloscope.

METHODS AND MATERIALS

1. *Clinical Material.*—Patients with valvular regurgitations were chosen for this study from among those who had been studied in the wards of the Philadelphia General Hospital or The Children's Hospital of Philadelphia and in whom an unequivocal episode of rheumatic carditis was diagnosed. The mur-

murs of these patients were recorded during subsidence of the disease, or later, during the quiescent phase, if there was well-established rheumatic heart disease with valvular insufficiency.

Patients with congenital heart disease were seen at the Hahnemann Hospital of Philadelphia through the courtesy of Dr. Daniel F. Downing. The diagnosis of the congenital cardiac lesion was in each case verified by angiocardiography, by cardiac catheterization, or by surgery.

The subjects whose cardiac murmurs were included in this study in the two categories of innocent murmurs were children who had been referred to the Rheumatic Fever Clinic of the Philadelphia General Hospital or of The Children's Hospital of Philadelphia because of an incidental finding of a cardiac murmur in the course of a routine examination by the school or the family physician.

These children had been studied on admission to these clinics by physical examination, electrocardiogram, 6-foot anteroposterior roentgenograms of the thorax, erythrocyte sedimentation rate, and serologic titrations of antistreptolysin and streptococcal antihyaluronidase. Although the results of all of these tests had given no indication of heart disease, most of these patients were seen thereafter in the clinic at intervals of a few months for at least three years. Several were observed for as long as five years, and three of those in the pulmonic-systolic group for eight years. In none of the patients presented in these two groups had any evidence of heart disease or rheumatic fever appeared during these periods of observation, nor were any changes observed except for diminution in intensity and distance of radiation of the murmurs.

The character and classification of each of the murmurs examined in this study, except those of patients with congenital heart disease, were verified by the independent observation of at least three physicians associated with this series of investigations. The criteria of classification, in the case of the two groups of innocent murmurs, were in accordance with the description of these murmurs as given in the introduction above.

2. *Instrumentation and Procedure.*—Heart sounds and murmurs were recorded in a quiet room by means of a specially adapted microphone. This consisted of a dynamic sensing element (from an Electrovoice model 647 microphone) mounted 1 to 2 mm. behind a Bakelite diaphragm (as used in diaphragm stethoscopes) with a closed air chamber between diaphragm and sensing element. The output of the microphone was fed into a Presto RC-7 amplifier and the signal was recorded on magnetic tape at 15 inches per second with a Presto A-920 recording head. During the recording the amplification was adjusted so that the peak amplitudes were as close to zero as possible on the VU meter provided with the instrument.

Suitable portions of this tape were then edited, eliminating breath sounds and artifacts. These were then spliced into loops of about 30 to 60 inches in circumference, which could be played repeatedly without interruption. The line output of the tape recorder was filtered through a low-frequency high-pass filter (−4 decibels at 70 c.p.s., and below that, 18 decibels per octave), in order to eliminate distortion due to very low-frequency vibrations. The output of this

filter was introduced into a DuMont 304A single-channel oscilloscope, using the 100 cycle signal of a Hewlett-Packard audio-oscillator as timing reference. The traces thus recorded were then photographed and enlarged for study.

RESULTS

1. *Precordial Vibratory Murmurs.*—Oscillograms of fifteen subjects with such cardiac murmurs were examined. Certain similarities could be noted within this group. The tracing of the murmur was separated by a slight gap from that of the first sound, then continued for a period usually in the range of one-third to one-half of systole. The amplitude of the murmur usually increased at first and then decreased, giving a roughly diamond-shaped envelope to the wave. At its maximum, the amplitude was never louder than the preceding first heart sound. Similarities in wave form were also noted among the tracings of precordial vibratory murmurs. These were among the relatively simpler forms found in this study, ranging from those which consisted almost entirely of an apparently regular wave to those which showed an apparently basic wave of this kind with a slight or moderate degree of distortion. The frequency of this apparently basic wave was not constant among the subjects examined within this group, but was found to be distributed over a range between 90 and 180 cycles per second. The distribution of the frequencies of this apparently simple wave which was found within this group is shown in Table I. Tracings typical of this group are shown in Fig. 1.

TABLE I. RELATIVE AND ABSOLUTE DURATION AND FREQUENCY OF THE APPARENTLY BASIC WAVE FOUND IN OSCILLOGRAPHS OF PRECORDIAL VIBRATORY MURMURS

SUBJECT		DURATION OF CARDIAC CYCLE (SECONDS)	DURATION OF MURMUR (SECONDS)	FREQUENCY OF THE APPARENTLY BASIC WAVE (CYCLES PER SECOND)
1.	M. D.	0.29	0.10	130
2.	L. F.	0.25	0.14	180
3.	K. H.	0.28	0.14	150
4.	A. B.	0.25	0.11	170
5.	D. W.	0.28	0.10	120
6.	D. S.	0.26	0.10	130
7.	H. E.	0.25	0.12	180
8.	W. B.	0.35	0.15	90
9.	J. L.	0.26	0.10	130
10.	G. P.	0.37	0.11	85
11.	G. G.	0.28	0.10	140
12.	M. D.	0.26	0.12	140
13.	C. M.	0.25	0.08	130
14.	M. G.	0.24	0.08	140
15.	L. K.	0.31	0.12	90

2. *Pulmonic-Systolic Murmurs.*—This cardiac murmur was studied in a group of fourteen subjects, none of whom had an apical systolic murmur. The tracings of this group of murmurs also showed similarities to each other and some similarities and differences to the group of precordial vibratory murmurs described above. In this group, also, the murmur was generally confined

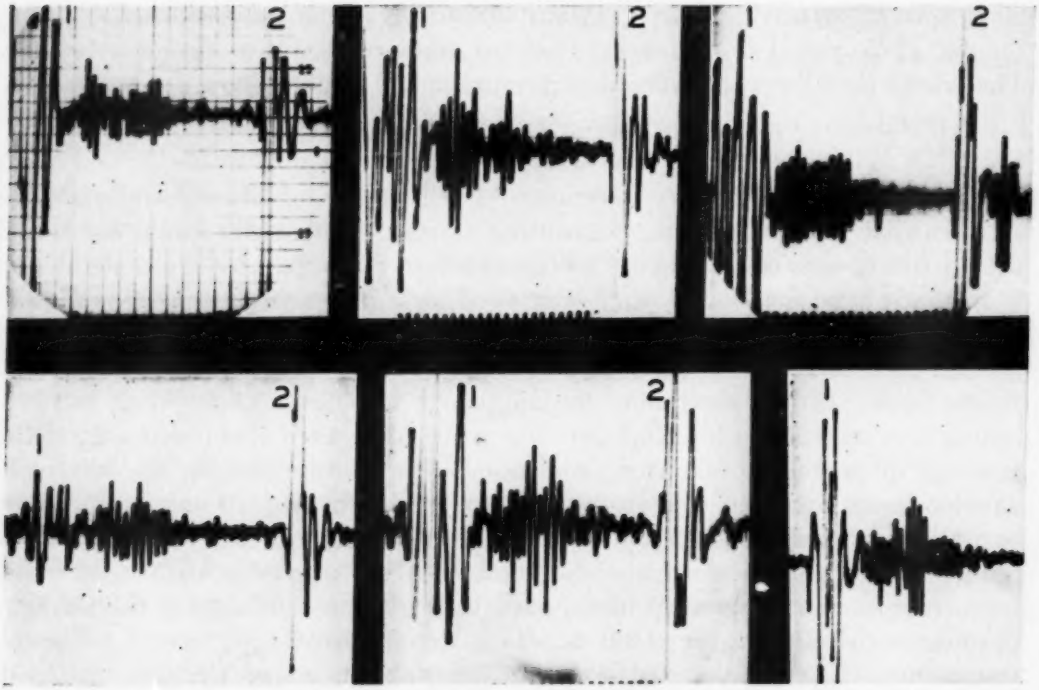

Fig. 1—Oscillographs of typical examples of the precordial vibratory murmur ("twanging-string murmur" of Still). Marker below each oscillograph indicates time in units of 0.01 second. The numbers 1 and 2 indicate the oscillations due to the first and second heart sounds, respectively.

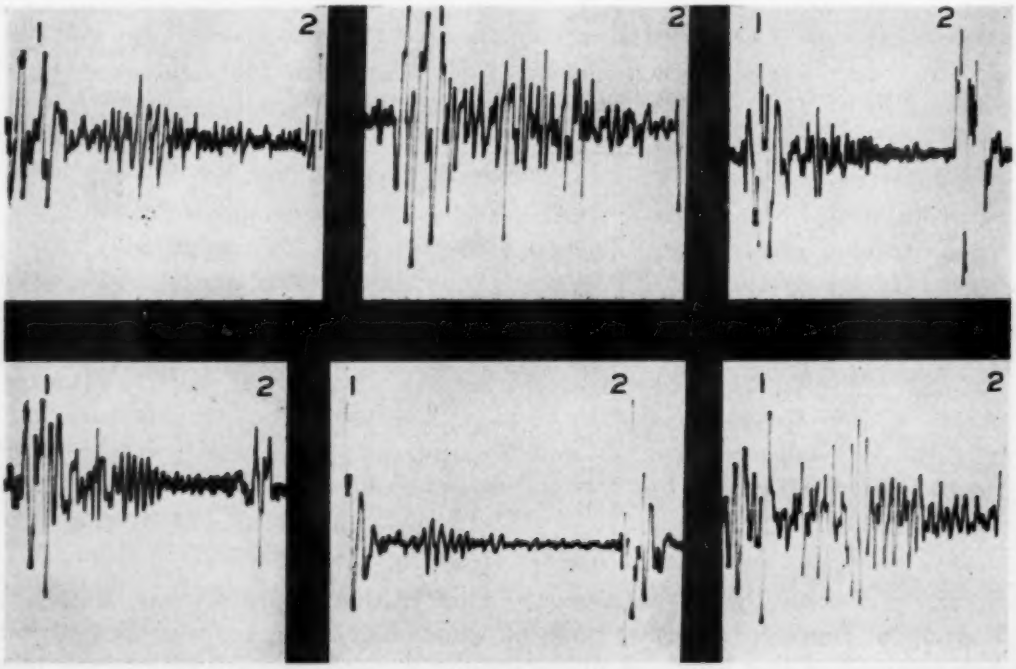

Fig. 2.—Oscillographs of typical examples of the other presumably innocent major murmur of childhood, the pulmonic-systolic murmur.

to the first third or half of systole, and usually showed a rising and then falling amplitude with some approximation to a diamond-shaped envelope. In the tracings of this group of murmurs a basic wave of uniform frequency and relatively simple form could be discerned. This form was, however, distorted in every case. The degree of this distortion varied over a given range which was clearly greater than the range of distortion found in the samples of precordial vibratory murmurs. The frequency of the apparently basic wave was found in these fourteen tracings to be within a range of 90 to 130 cycles per second; the distribution of these is shown in Table II. Typical oscillographs of this roup of murmurs are shown in Fig. 2.

TABLE II. RELATIVE AND ABSOLUTE DURATION AND FREQUENCY OF THE APPARENTLY BASIC WAVE FOUND IN OSCILLOGRAPHS OF PULMONIC-SYSTOLIC MURMURS

	NAME	DURATION		FREQUENCY OF APPARENTLY BASIC "CARRIER WAVE"
		CYCLE	MURMUR	
1.	L. W.	.30	.11	110
2.	N. J.	.32	.10	110
3.	B. H.	.30	.15	110
4.	H. D.	.35	.20	120
5.	H. C.	.30	.14	130
6.	B. C.	.40	.25	90
7.	L. K.	.33	.11	130
8.	G. D.	.35	.10	130
9.	H. J.	.31	.15	110
10.	M. L.	.32	.12	120
11.	D. M.	.30	.21	120
12.	J. C.	.30	.15	100
13.	R. K.	.33	.16	100
14.	M. C.	.33	.13	100

The tracings described above were taken of subjects without apical systolic murmurs. Loud apical systolic murmurs can, not infrequently, be heard with progressively decreasing intensity as far as the pulmonic area, and in the interests of the best physical description of the pulmonic-systolic murmur it was desirable to avoid contamination with audible or subaudible vibrations due to another cardiac murmur. Tape recordings were also taken at the pulmonic area of subjects who had, before the recording, been classified as having both a pulmonic-systolic and an apical systolic murmur. Of oscillographs of sixteen such recordings, eleven showed a discernible, apparently basic wave, but with a much higher range of distortion than in the case of the pulmonic systolic murmurs recorded in children with no other murmurs. In the remaining five oscillographs no such pattern could be discerned. Of the sixteen tracings four showed murmurs confined to early systole; the remainder extended throughout this place of the cardiac cycle.

3. *Murmurs of Mitral Regurgitation.*—Oscillographic tracings of apical systolic murmurs were examined in patients known to have mitral insufficiency.

All of the thirty-two such oscillographs examined showed certain characteristics in common which were different from those of the two groups of murmurs described above. Almost all of the apical systolic murmurs extended throughout systole, ending at the second heart sound. In a few instances the amplitude rose during the first part of the murmur, and then fell, but the great majority of these murmurs showed no consistent increase or decrease in amplitude throughout the murmur. The wave forms observed in these oscillograms were very complex, to the extent that no single component of given frequency was recognizable, nor could any pattern or repeated unit be detected in these tracings. Typical oscillograms of murmurs of mitral regurgitation are shown in Fig. 3.

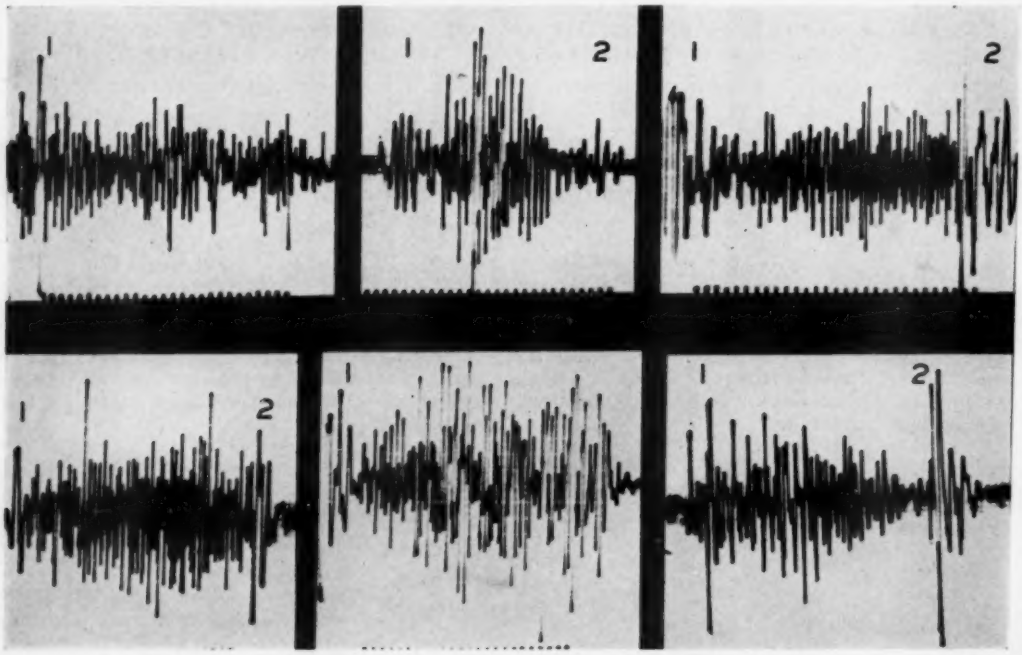

Fig. 3.—Oscillographs of typical murmurs of mitral insufficiency.

4. *Murmurs of Aortic Regurgitation.*—Recordings of heart sounds and murmurs were obtained from twenty-four patients with aortic insufficiency. The oscillograms showed that these murmurs began directly from the second heart sound and extended through diastole, usually until the next first heart sound. The amplitude of the murmur usually showed a progressive decrease during the period of the murmur. The wave form was generally similar to that found in the oscillographs of the murmurs of mitral insufficiency, being at least as complex as in the case of those murmurs. In fact, there was an impression of an even greater degree of irregularity in the tracings of the murmurs of aortic insufficiency than in those of mitral insufficiency (Fig. 4).

5. *Some Murmurs Due to Congenital Cardiac Malformations.*—A sampling of tape recordings was also made of patients with congenital heart disease. These were confined, for purposes of this study, to malformations which produce systolic murmurs audible in the second or third intercostal spaces at the left border of the sternum, and the tape recordings were taken at that area.

Of the patients examined, the majority had interventricular septal defects or the tetralogy of Fallot. Pulmonic stenosis, interatrial septal defects, and patent ductus arteriosus were less common, and there were scattered cases of coarctation of the aorta, tricuspid atresia, and aortic stenosis. The oscillograms of the systolic murmurs of the entire group showed certain similarities, regardless of the lesion present. The amplitude of these murmurs was usually

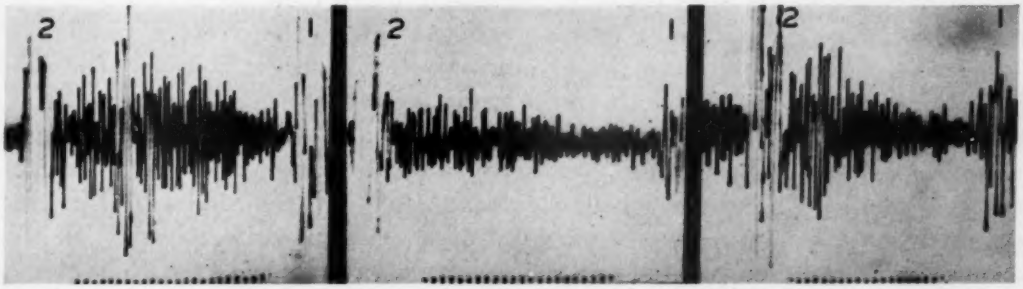

Fig. 4.—Oscillographs of murmurs of aortic insufficiency.

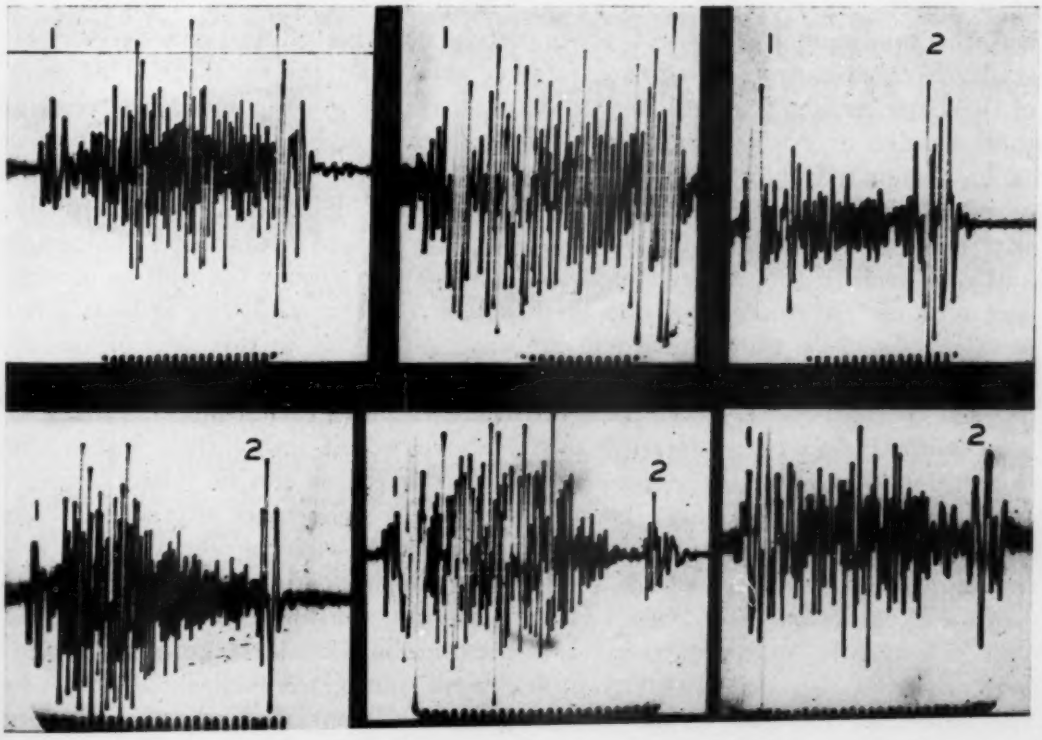

Fig. 5.—Typical oscillographs of murmurs of congenital cardiac lesions, taken at the second or third intercostal spaces at the left sternal border. The tracings shown are murmurs due to the following lesions: Left to right, top row: interventricular septal defect, coarctation of aorta, interatrial septal defect; lower row: tetralogy of Fallot, aortic stenosis, pulmonic stenosis.

quite high, relative to the heart sounds, although a substantial range of intensity was seen. The amplitude of the murmur usually showed no tendency to change in the course of the murmur. In terms of wave form, these oscillo-

grams also showed similarities within the group. They were highly complex, the complexity being again, perhaps, greater than in the case of the murmurs of mitral insufficiency examined, so that no discernible pattern or basic frequency could be detected (Fig. 5).

DISCUSSION

Any implications from the data presented above must be drawn with due regard for certain limitations or reservations. First, the average number of specimens of the respective types of murmurs is not large; however, the data have been presented at this stage of the study because the fairly uniform character of the specimens within the respective type of cardiac murmurs would suggest that in each of these a representative sample has been obtained. Second, the evidence for the nonpathologic significance of the precordial vibratory and pulmonic-systolic murmurs is essentially of a circumstantial nature. In this connection it must be pointed out that evidence of nonpathologic character of a physical sign would inevitably be circumstantial, since one can only demonstrate absence of abnormal function within the available range of methods of testing the organ system involved. In the present study a few of the patients had the minimum evidence of a completely negative clinical and laboratory study on consultation, as indicated above. However, the substantial majority of these patients had, in addition, some years of follow-up in specialized clinics; these totaled over 70 patient-years for the two groups of patients designated as having nonpathologic murmurs. Finally, in terms of the auditory recognition of these two presumably innocent murmurs, it should be pointed out that these murmurs are well recognized among trained pediatric cardiologists, and that each of the children included in these two groups (as well as others) was examined, in connection with their inclusion in this study, by at least three physicians, two of whom have had intensive experience in this field of auscultation for at least ten years.

On the basis of an acceptance of these two types of murmurs as being in fact nonpathologic, the data presented above would imply that within the population of each murmur sampled certain differences can be noted between wave forms of the innocent and of the pathologic murmurs studied: in the former the presence of an apparently simple basic wave of relatively low frequency can be discerned, which is subject to varying degrees of distortion, less so in the case of the precordial vibratory murmur and more in the case of the pulmonic-systolic; on the other hand, in the samplings of all the groups of pathologic murmurs studied highly complex wave forms were characteristic. In the latter case the form of the wave is quite consistent with what is generally accepted as the physical basis of the organic cardiac murmur—a jet of fluid through a relatively narrow orifice under conditions which give rise to turbulence. In the case of the innocent murmurs of childhood the mechanism is not yet known. A possibility which is suggested by the wave forms of these innocent murmurs is that they may be due to free vibration of some anatomic structure in the heart, this vibration being caused by the impact of a fluid mass or sudden pressure change in the course of the normal hydrodynamic changes in the heart.

In terms of this concept the vibration of such a structure at its natural period would account for the basic wave, and the distortions would be due to other vibrations, some perhaps secondary to the basic one.

Such a hypothesis as to the genesis of many of the functional murmurs of childhood is of course entirely speculative, and rests only on consistency with geometric forms of waves as reported in this study. It may, however, have some value in suggesting further studies of physical parameters of innocent and organic murmurs, such as the analysis of the higher-frequency distorting elements found in the innocent murmurs in terms of harmonic or unrelated frequencies relative to the basic wave, examination of the organic murmurs by oscillograms amplified along the horizontal axis (the resolving power of the oscilloscope in these murmurs has not fully been exploited in this study because the primary interest in a comparison of these with the functional murmurs indicated a degree of X-axis "spread" of the same order per unit time for all murmurs examined), or study of the frequency distribution of the vibrational energy of both innocent and organic murmurs by such means as sound spectrography or electronic filtration.

SUMMARY

Cardiac murmurs of several types found in children and adolescents have been recorded on magnetic tape and examined by cathode-ray oscillography. The types of murmurs studied have included two presumably innocent types of murmurs, the precordial vibratory ("twanging-string" murmur of Still) and the pulmonic-systolic murmur, which comprise the great majority of nonpathologic murmurs of childhood, and several types of organic murmurs, those due to aortic and mitral insufficiency and to a variety of congenital malformations.

In terms of wave form, the precordial vibratory murmurs examined showed a discernible basic wave of frequency ranging from 90 to 180 cycles per second, among various subjects, with a small and variable degree of distortion. In oscillograms of pulmonic-systolic murmurs a basic wave in the range of frequency given above could also be discerned, but the degree of distortion was noticeably greater than that found in the precordial vibratory murmurs. In the case of the specimens examined in all the groups of organic murmurs mentioned above the wave forms were highly complex, with no detectable basic wave or recognizable pattern. A possible implication of these differences in wave form is discussed.

This study was carried out with an oscilloscope and camera presented to the Rheumatic Fever Research Laboratory of The Children's Hospital of Philadelphia in memory of Dr. C. Leslie Cushman, Associate Superintendent of Schools of Philadelphia.

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CALCIFICATION OF THE PERICARDIUM CAUSED BY A HITHERTO UNRECOGNIZED ETIOLOGICAL FACTOR

MORRIS KLEINFELD, M.D.,* AND CHARLES P. GIEL, M.D.**

NEW YORK, N. Y.

CALCIFICATION of the pericardium has been associated with diseases of varied etiology. However, in the majority of cases the etiological agent remains undefined. The most frequently recognized causes are tuberculosis, rheumatic fever, septic infections, and nonspecific pericarditis. Of lesser incidence are trauma, neoplasm, foreign body, and myocardial infarction.[1-3] Recently, histoplasmosis has been suggested as another agent responsible for calcification of the pericardium.[4]

In a recent clinicoroentgenologic study of workers employed in talc mills and mines by one of the authors (M.K.), calcification of the pericardium was observed in three of thirty-seven cases.[5] It is the purpose of this paper (a) to present these three cases with calcification of the pericardium, (b) to establish another etiological agent (inhalation of talc) for pericardial calcification, and (c) to discuss the possible mechanisms responsible for the latter.

CASE REPORTS

CASE 1.—B. M., a 79-year-old man, was first seen by the authors in August of 1954, at which time his chief symptoms were moderate productive cough and exertional dyspnea. These symptoms were first observed by the patient in 1947 and had progressed only minimally since. Prior to the onset of these symptoms he had been in good health. A review of systems was essentially noncontributory. The patient denied any past history of chest trauma, episodes of unexplained or prolonged fever, hypertension, rheumatic fever, or tuberculosis. There was no history of any surgery.

Occupational History.—For twenty-four years prior to his retirement in 1943 he had worked as a mucker in a talc mill where exposure to talc dust was rather high. For six years prior to this employment he had been a miner of iron pyrites.

Clinical Findings.—The patient appeared well developed, well nourished, and of good color. His neck veins were not congested. His chest was emphysematous and his chest expansion was limited to one inch. There was marked dorsal kyphosis. With the exception of coarse inspiratory râles present at both bases, the lungs were relatively clear. The heart was not enlarged and the sounds were distant. A_2 was slightly louder than P_2. The rhythm was regular and no murmurs were audible. Abdominal examination was essentially normal. There was no peripheral edema. The fingers and toes showed a moderate degree of clubbing. The reflexes were physiologic.

Laboratory Data.—The chest roentgenogram taken Sept. 24, 1954 (anteroposterior view), showed a moderate degree of infiltration bilaterally, located mainly in the mid-lung fields. Dense, opaque plaques were present along both leaves of the diaphragm. The costophrenic angles were clear. The heart was of normal size and contour. Extending along the upper third of the left border of the heart was a fine rim of calcium (Figs. 1 and 2).

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*Chief, Medical Unit, Division of Industrial Hygiene, New York State Department of Labor.

**Senior Physician, Division of Industrial Hygiene, New York State Department of Labor.

Re-examination of the patient on Sept. 22, 1955, disclosed that he had additional symptoms, namely incontinence, weakness, and mild anterior chest pain. The clinical findings were essentially similar to those in August, 1954, with the exception of minimal ankle edema and unsteadiness of gait. Deep reflexes and position sense were normal and Romberg was absent. A chest x-ray was not obtained at this time. The electrocardiogram showed a normal sinus rhythm with occasional nodal premature systoles. The size, shape, and configuration of the complexes were normal.

He was placed on aminophylline and nitroglycerine. The former afforded some relief of his dyspnea. The nitroglycerine was without effect on his chest pain.

CASE 2.—L. A., a 68-year-old white man, was first seen by us in 1940 when his chief complaints were weight loss, night sweats, productive cough, and anterior chest pain. The latter did not radiate and was not precipitated or worsened by effort. The patient noted the onset of these symptoms in 1933. The night sweats subsided after two months, and there was a gradual regain in his weight. The cough persisted and became productive in 1939. The chest pain continued but was intermittent in character and was unrelieved by nitroglycerine. Systemic review was essentially noncontributory. He denied any history of chest trauma, unexplained or prolonged fever, rheumatic fever, tuberculosis, or hypertension.

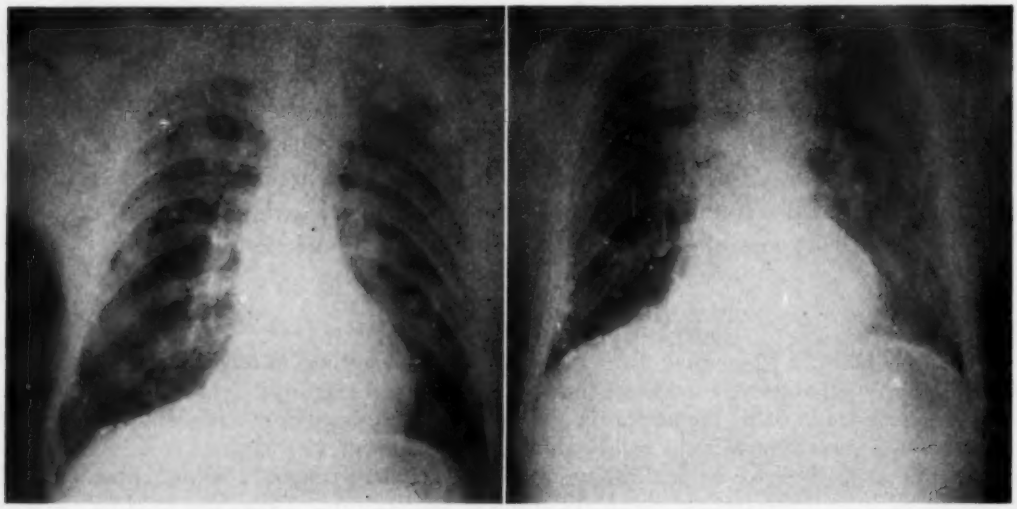

Fig. 1. Fig. 2.

Fig. 1.—Posteroanterior view of the chest in Case 1 taken in 1940 showing the calcification along the upper left heart border. Note the diaphragmatic calcifications and the pulmonary infiltrations characteristic of talc pneumoconiosis.

Fig. 2.—Repeat chest film in Case 1 taken in 1954 showing the extent of pericardial calcification unchanged. Note the new pleural calcification of the left and the slow progression of the pulmonary infiltrations as described in the text.

Occupational History.—From 1924 to 1940 he was employed as a talc miller, and for thirty-one years prior to this he was a mucker in the talc mines.

Clinical Findings.—He appeared to be fairly well developed and well nourished. His color was good. There was no congestion of the neck veins. The breath sounds were diminished at the bases and there was dullness to percussion over both apices. Chest expansion was good. The heart did not appear to be enlarged and the rhythm was regular. The heart sounds were of good quality and no murmurs were audible. Abdominal examination was essentially negative. There was no peripheral edema or clubbing. The reflexes were physiologic.

Laboratory Findings.—Chest roentgenogram of July 1, 1940, showed dense pulmonary shadows of varying size, more conspicuous in the left lung. Along the left leaf of the diaphragm was a dense longitudinal plaque of approximately 3 cm. in length. The costophrenic angles were clear. The heart was of normal contour and size. The ascending aorta was elongated. There was a rim of calcification measuring 3 cm. in length along the left border of the heart and this was also

well delineated in the left anterior oblique position (Figs. 3 and 4). The electrocardiogram (limb leads) was essentially normal.

He was given aminophylline and expectorants with minimal improvement of his dyspnea. For the subsequent five years, he showed very little progression of his symptoms and his clinical findings were essentially unchanged. On Aug. 12, 1945, he sustained a skull fracture following which he lapsed into a coma and died. No autopsy was obtained.

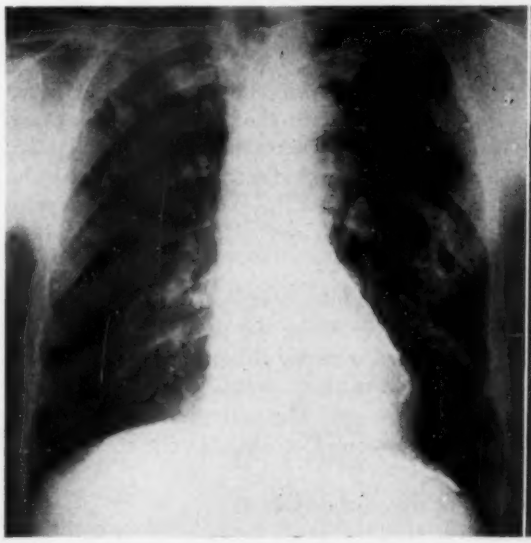

Fig. 3.

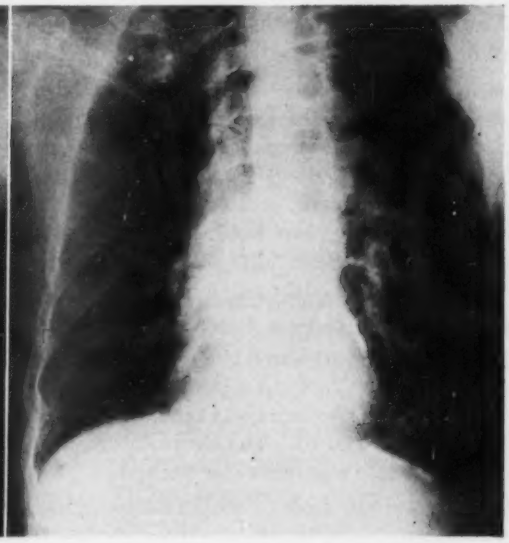

Fig. 4.

Fig. 3.—Posteroanterior view of the chest in Case 2 taken in 1940 showing dense calcification along the upper left border of the heart. Note the diaphragmatic and pleural calcifications and the pulmonary infiltrations.

Fig. 4.—Oblique view in Case 2 showing that the calcification involves the pericardial surface.

Fig. 5.

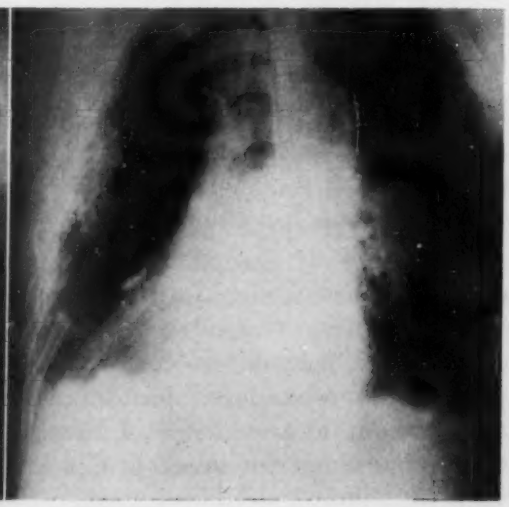

Fig. 6.

Fig. 5.—Posteroanterior view of chest taken in Case 3 showing a small area of dense calcification on the upper right border of the heart. Note again the diaphragmatic and pleural calcifications and the pulmonary infiltrations.

Fig. 6.—Oblique view in Case 3 showing that the calcified area involves the pericardial surface.

CASE 3.—A. G., a 64-year-old white man, was first seen by us in 1940, at which time he complained of productive cough and easy fatigue of three years' and two years' duration, respectively. These symptoms had not progressed. A review of systems was not contributory except for frequent colds. The patient denied any history of cardiac disease, chest trauma, rheumatic fever, tuberculosis, or periods of unexplained fever. With the exception of pneumonia at age 12, he had been in good health.

Occupational History.—He worked in the same talc mills and mines as the other workers described above for thirteen and twenty-one years, respectively. For three years prior to that he was employed as a zinc miner.

Clinical Findings.—He appeared well developed and well nourished and of good color. There was no congestion of his neck veins and no masses were palpable in the neck. His chest was barrel-shaped, but expansion was adequate. The lungs were hyperresonant with basal râles predominantly in the left lung. The heart was not enlarged. The rhythm was regular with the exception of frequent, premature, ventricular systoles. A_2 was equal to P_2. The heart sounds were of good quality. There were no abnormal findings in the abdomen. There was no evident clubbing present. The reflexes were physiologic.

Laboratory Data.—Chest roentgenogram revealed small nodules scattered throughout both lung fields and extensive platelike pleural densities bilaterally. Along the superior lateral right border of the heart was a rim of dense calcification. In the left anterior oblique view this density was located on the right anterolateral surface of the heart. The aortic arch also showed a rim of calcification. The heart was otherwise of normal size and contour. The costophrenic angles were clear (Figs. 5 and 6). The electrocardiogram, with the exception of occasional premature ventricular systoles, was otherwise normal.

Several attempts to obtain follow-up on the patient were unsuccessful.

DISCUSSION

The incidence of pericardial calcification obtained from autopsy data varies from 0.17 to 0.38 per cent.[6,7] It is of interest that one-third of all patients in whom adhesive pericardial disease can be demonstrated show calcification of the pericardium on roentgenogram.[1] The finding of calcification is a valuable sign in the diagnosis of adhesive pericardial disease.

The three cases reported present a number of interesting features which warrant comment:

1. *Duration of Calcification of the Pericardium.*—In one case, B.M., the pericardial calcification was known to have existed for at least fifteen years, and in another, L.A., for a minimum of five years.

2. *Lack of Symptoms.*—In all three cases, the pericardial calcification persisted without significant changes in cardiac size or evidence of disturbed hemodynamics. One of the three cases had clubbing of the fingers due to lung disease. Mathewson[8] recently reported five patients with calcification of the pericardium of undetermined etiology whose courses were relatively benign and without any evidence of cardiac dysfunction. Although calcification of the pericardium can be of benign character, it is more commonly associated with the clinical picture of cardiac compression.[9-11]

3. *Age Group.*—The relatively advanced age of these cases (79, 68, 64) is in contrast to that found in chronic constrictive pericarditis with calcification where the age group reported has varied from 10 to 59 years.[10]

4. *Cardiac Size.*—The absence of cardiac enlargement in these three patients is of interest. This has also been noted by others. Harrison and White[12] reported that five out of their sixteen cases of chronic constrictive pericarditis with calcification showed normal cardiac mensuration.

5. *Electrocardiographic Changes.*—With the exception of Case 1, who showed a normal sinus rhythm with occasional nodal premature systoles, the electrocardiographic patterns were essentially normal. This is at variance with the observations of Mathewson[8] who reported depression of S-T segments and inverted T waves in all of his cases of benign calcification of the pericardium. The electrocardiographic abnormalities associated with constrictive pericarditis are well known.

The difficulty in determining the exact etiological agent is also apparent in these three patients. It is worth mentioning that in spite of the availability of sections of pericardium for microscopic study in forty-six of fifty-three cases of chronic constrictive pericarditis with and without calcification reported by Paul and associates,[10] the exact etiological diagnosis could not be ascertained in 56 per cent. In our cases, such causes as trauma, neoplasm, myocardial infarction, rheumatic fever, and histoplasmosis were believed remote. This is based on the history, clinical findings, laboratory data including the electrocardiogram and chest x-ray, and the clinical course. A tuberculous etiology cannot be entirely ruled out in Patient L.A. It is, however, more probable that the calcification is related to the inhalation of talc. The presence of calcification on other serosal surfaces such as the diaphragmatic pleura present in these three patients, as well as its frequent occurrence in other talc workers as observed by several investigators[5,13,14] strongly favors a similar etiology for the calcification of the pericardium.

The clinical picture presented by these patients revealed a chronic slowly progressive course with the predominant symptoms of pulmonary insufficiency consistent with the average course of talc pneumoconiosis.[5] This picture contrasts with that of constrictive pericarditis where the symptoms are of cardiac origin. None of our patients showed any evidence of right or left heart failure. The precordial pain present in our patients similarly did not appear to be of cardiac origin although one cannot entirely rule it out. The lack of response to nitroglycerine, the absence of any intensifying effect of effort, and the normal electrocardiograms after at least five years of chest pain would tend to exclude angina pectoris.

The exact mechanism responsible for the calcification of the pericardium in talc exposure is not known. Several mechanisms have been postulated to explain its occurrence on the diaphragm: (1) A direct mechanical effect of the talc fiber on the serosal surface resulting in an inflammatory response and capillary hemorrhages with subsequent deposition of calcium; (2) The lodging of talc particles in the lymphatics resulting in a characteristic inflammatory and granulomatous reaction followed by calcification at the inflammatory site.[13]

It would appear to the authors that the calcification of the pericardium can best be explained by a mechanical effect of the talc fibers resulting in a chronic inflammatory response and increased capillary hemorrhage with subsequent calcium deposition.

SUMMARY AND CONCLUSIONS

1. Three cases of calcification of the pericardium occurring in individuals chronically exposed to talc dust are described.

2. Inhalation of talc dust is presented as a hitherto unrecognized factor in calcification of the pericardium. Other causes such as tuberculosis, rheumatic fever, pericarditis, septic infections, etc., were reasonably excluded. The finding of calcification on other serosal surfaces (diaphragm and pleura) in pulmonary talcosis strongly supports a similar etiology for calcification of the pericardium.

3. Such interesting features as the advanced age of these patients, the long-standing presence of asymptomatic pericardial calcification, the normal heart size, and the absence of significant electrocardiographic changes are evaluated.

4. The mechanical effect of the talc fibers resulting in chronic inflammation and capillary hemorrhage with calcium deposition is postulated as a possible mechanism for the calcification of the pericardium.

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THE IMPORTANCE OF A TIGHT BLOOD PRESSURE CUFF

WILLIAM F. NUESSLE, M.D.*

MINNEAPOLIS, MINN.

WHEN taking blood pressure, The American Heart Association recommends that the deflated bag and cuff should be applied evenly and snugly around the arm.[1] Casual application of a loose cuff is a common error in blood pressure determination, especially with the newer clip-on cuffs. A study was undertaken to determine what differences arose when cuffs were applied loosely.

METHODS

Blood pressure determinations were made on one hundred individuals during examinations for employment and insurance. Pressures were obtained with a clip-on cuff applied tightly, and then redetermined with the cuff loosened so that its circumference was extended 3.1 cm.

RESULTS

There was a general increase in systolic and diastolic levels using the loosened cuff. Higher readings were found in ninety-four instances. The mean systolic increase was 8.1 mm. Hg and diastolic 9.3 mm. The degree of change was approximately the same in the forty-three men and fifty-seven women. The change was greater in persons of average or heavy build. This may be illustrated by grouping the individuals in categories varying by 15-pound increments from ideal weight (Table I). The mean change for the sixty average and heavy individuals was 9.8 mm. Hg systolic and 11.5 diastolic. The change in the forty lean persons was 5.4 mm. Hg systolic and 6.5 diastolic.

DISCUSSION

The principle employed in the indirect measurement of blood pressure consists of balancing air pressure against the pressure of the blood in the brachial artery and then estimating the former by means of a manometer.[2] The inflatable bag should be 20 per cent wider than the diameter of the arm or thigh on which it is to be used.[1] In the conventional arm cuff the bag measures 12 by 23 cm. Narrower arm cuffs such as the Riva-Rocci band give "high" reading.[3] Pediatric cuffs applied to the adult arm and arm cuffs applied to the leg give similar findings.[4,5] Cuffs which are relatively too broad give "low" readings.[6,7]

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*Assistant Medical Director, Prudential Insurance Company of America.

TABLE I. BLOOD PRESSURE INCREASE USING LOOSE CUFF IN INDIVIDUALS GROUPED ACCORDING TO IDEAL WEIGHT FOR THEIR HEIGHT

CATEGORY	NUMBER OF INDIVIDUALS	MEAN SYSTOLIC CHANGE (MM. HG.)	MEAN DIASTOLIC CHANGE (MM. HG.)
More than 30 pounds overweight	6	12.3	11.3
16 to 30 pounds overweight	10	10.0	8.8
Ideal weight to 15 pounds overweight	19	10.2	11.9
Ideal weight to 15 pounds underweight	25	8.6	12.3
16 to 30 pounds underweight	26	5.0	6.1
More than 30 pounds underweight	14	6.3	7.1

Thomson and Doupe[8] measured tissue pressures under inflated cuffs. They found pressures equal to the manometric only near the center of the cuff. The tissue pressure in the lateral margins of the cuff was less than that recorded in the manometer. The zone of effective pressure narrowed at greater depths in the tissues. At the depth of bone the margin of ineffective pressure extended 6 cm. from the edge of the cuff. It may be assumed that if the brachial artery is being compressed by this margin because of a rotated or narrow cuff, greater manometric pressures will be necessary to occlude the vessel, and "high" readings will result.

Bazett and Laplace[9] emphasized the importance of a tight cuff. They indicated that "high" readings will otherwise be obtained because of pressure wasted in distention of the rubber. This reasoning can be disputed by placing the cuff on a table and inflating the bag to a volume exceeding that under a loose cuff. No pressure is recorded.

It is suggested that a loose cuff gives high readings because of the central ballooning of the bag, which exerts the pressure-effect of a narrow cuff with effective longitudinal axis shortened as well. This can be exemplified by recording pressures during rotation of the cuff in the four quarters of the arm. Little change occurs in the small arm. In the large arm, "high" levels are obtained when the bag is opposite the brachial artery. This effect can be magnified by using a loose cuff. Another illustration is that of placing a cuff around a limb and partially inflating. If a second cuff is wrapped tightly and then loosely over the first cuff, air pressure introduced in the second will have a greater effect on the first when tight than when loose.

It is sometimes difficult to apply clip-type cuffs on heavy arms so that the inflatable bag compresses the brachial artery directly. However, it is in these individuals where direct pressure with a tightly-wrapped bag is most important, for in the deeper tissues there is a diminished zone of pressure equal to the manometric air pressure.

SUMMARY

Loosely applied blood pressure cuffs gave high readings with a mean increase of 8.1 mm. systolic and 9.3 mm. diastolic. This effect was augmented in people with large arms. Care should be taken to apply cuffs so the brachial artery is directly compressed by the mid-portion of the tightly-bound inflatable bag.

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Clinical Reports

CHLOROQUINE

Clinical and Electrocardiographic Observations After Intravenous Administration in Two Cases of Auricular Fibrillation

L. M. Sanghvi, M.R.C.P. (London), D.T.M.& H. (England)

Jaipur, India

ANTIMALARIAL drugs quinine, quinidine, and Atabrine have been known to have definite action on the heart and have been used for treatment of cardiac arrhythmias. Value of quinine was not generally known until it was rediscovered by Wenckebach in 1914. In 1918 quinidine, another alkaloid of the Cinchona bark, was found by Frey to be more effective than quinine in the treatment of cardiac arrhythmias and is now universally used for this purpose. Atabrine, a synthetic antimalarial, abolished auricular fibrillation in the dog.[4] Clinically Atabrine has been successfully employed in the treatment of auricular fibrillation and paroxysmal tachycardia.[5] Arora[1] observed that the cardiac action of antimalarials ran almost parallel to their antiveratrinic action, and that the antiveratrinic action of chloroquine and Camoquin was more marked than mepacrine. Arora and associates[2] found chloroquine more effective in its antifibrillatory action than quinidine in animal experiments. The object of this paper is to report clinical and electrocardiographic observations after intravenous administration of chloroquine in two patients with auricular fibrillation.

The drug used for intravenous injection was Resochin (Bayer) containing 30 mg. of chloroquine base per cubic centimeter. The solution was injected undiluted intravenously at the rate of 2 c.c. per minute and the maximum dose injected did not exceed 9 mg. per kilogram body weight. ECG tracings were recorded just before the injection, continuously during the injection, and for a further period of thirty minutes, and then at intervals.

Case 1.—A woman aged 50 years was admitted to the hospital for severe congestive cardiac failure. She had auricular fibrillation and, as there was no evidence of valvular lesion or any other cause, it appeared to be due to coronary atherosclerosis. Her cardiac failure was treated with Digoxin, mercurial diuretics, and salt-free diet. At the time of trial of chloroquine she was fully compensated and digitalized, the auricular rate being 440 and ventricular rate 80 per minute, her blood pressure 110/75 mm. Hg, and weight 92 pounds.

After injection of 250 mg. of chloroquine base, fibrillation changed to flutter, auricular rate slowing to 280 per minute, while the ventricular rate increased to 150 per minute (Fig. 1). Further injection produced ventricular premature beats, and runs of paroxysmal ventricular tachycardia

From the Department of Cardiology, S.M.S. Medical College and Hospital, Jaipur, India.
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appeared when 400 mg. of the drug was injected. At this time the patient complained of severe palpitation and sweated profusely. There was severe nausea and she vomited once. She felt giddy, and became disorientated and less responsive to questions. Blood pressure fell from 110/75 to 100/65 mm. Hg. After twenty minutes, the premature beats ceased and flutter fibrillation or impure flutter appeared. In another five minutes fibrillation returned. The patient now felt otherwise all right except for slight weakness. Blood pressure returned to preinjection level,

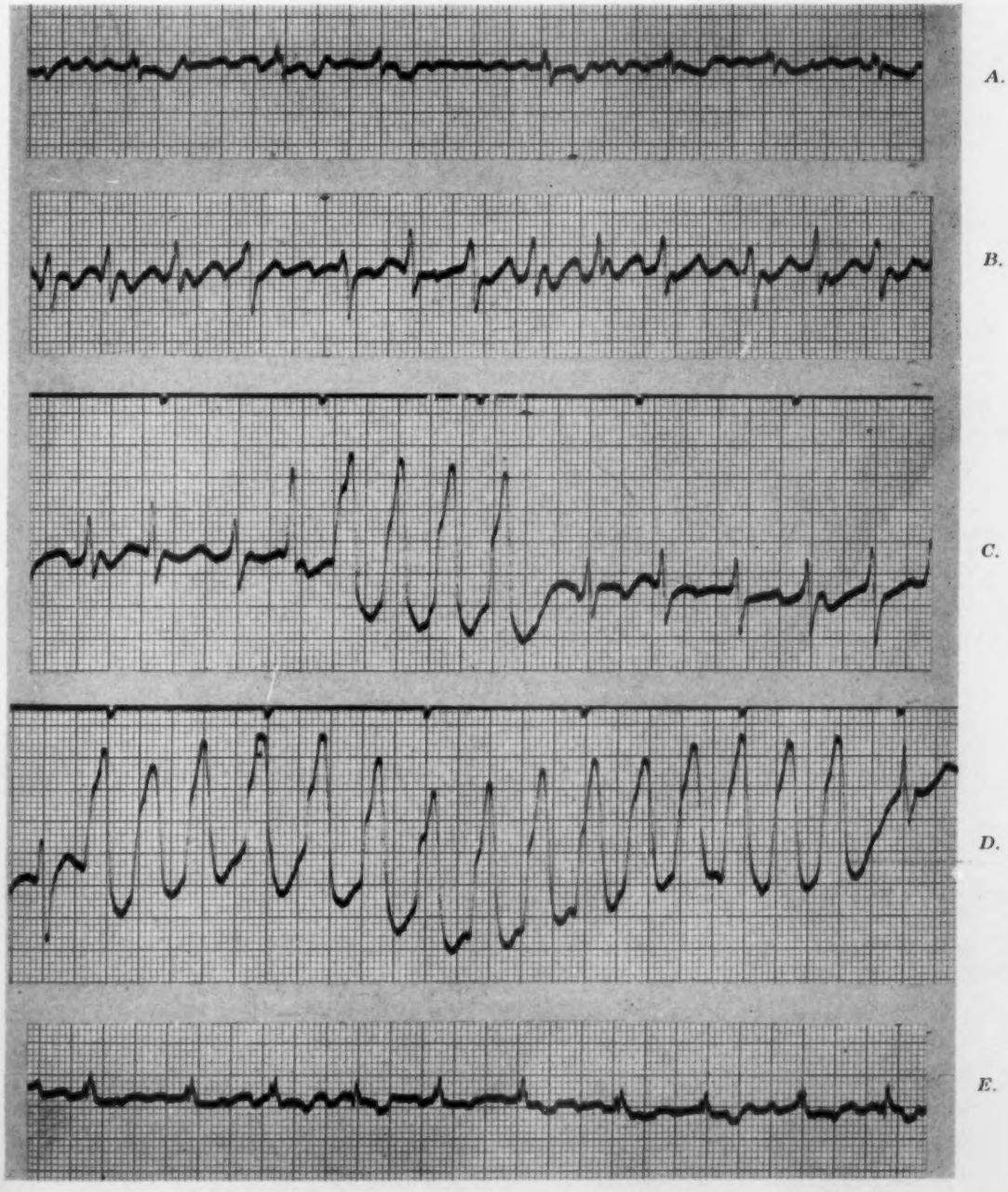


Fig. 1.—Lead V_1. *A*, Before injection, showing fibrillation; *B*, After 250 mg., flutter and increased ventricular rate; *C* and *D*, After 400 mg., ventricular premature beats and paroxysmal tachycardia; *E*, After 25 minutes, reversal to fibrillation.

but slight tachycardia persisted for thirty-six hours. Subsequently quinidine orally administered converted fibrillation to normal sinus rhythm in seventy-two hours.

CASE 2.—A man aged 30 years, weighing 106 pounds, had rheumatic mitral stenosis and auricular fibrillation without any cardiac failure. He was admitted to the hospital with palpitation. Before the injection the auricular rate was 450 and ventricular rate 68 per minute and the blood pressure 120/90 mm. Hg.

After injection of 250 mg. of chloroquine base rhythm changed from fibrillation to flutter with an auricular rate of 300 and ventricular rate of 108 per minute. With further injection

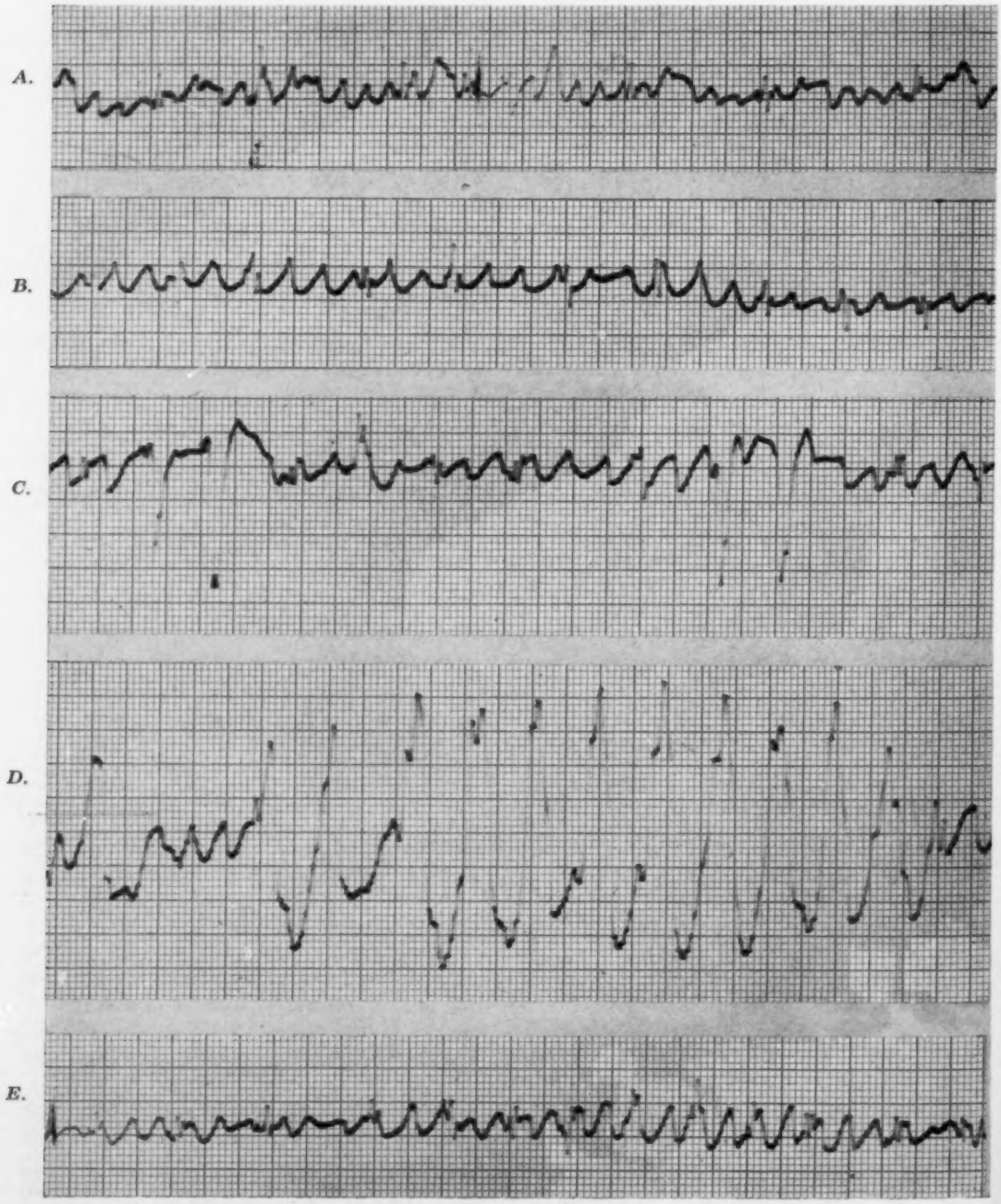
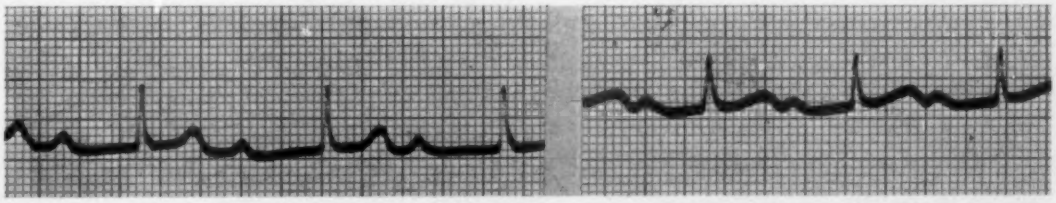


Fig. 2.—Lead V_1. *A*, Before injection, fibrillation; *B*, After 250 mg., flutter. *C* and *D*, After 450 mg., flutter, ventricular premature beats, and paroxysmal tachycardia; *E*, After 15 minutes, flutter fibrillation.

isolated ventricular premature beats appeared, and when 450 mg. was given, these beats appeared in groups and sometimes in greater numbers presenting short periods of paroxysmal tachycardia (Fig. 2). The patient complained of annoying palpitation and giddiness, sweat appeared on the forehead and extremities, and he became listless and drowsy, felt very weak as if paralyzed, and became less responsive to questions. Blood pressure fell from 120/90 to 100/80 mm. Hg. The premature beats ceased to appear after fifteen minutes, and the rhythm changed to impure flutter. This then reverted to fibrillation in another ten minutes. The patient then felt all right and the blood pressure returned to the preinjection level, but the tachycardia persisted for forty-eight hours before the ventricular rate returned to the slow preinjection level. An attempt was later made to convert fibrillation to normal rhythm by oral quinidine therapy. As with chloroquine, quinidine changed fibrillation to flutter with rapid ventricular rate, but premature beats and ventricular tachycardia did not appear. Flutter however could not be converted to sinus rhythm in spite of intensive quinidine therapy which ultimately had to be stopped because of rapid ventricular rate and distressing palpitation.

It was observed that in both the above cases, the auricular rate slowed down though only to a certain extent. It seemed that this was probably due to a vagolytic action of the drug, similar to quinidine, which increases the refractory period of the auricular musculature. It was therefore decided to find out the effect of the drug in partial auriculoventricular heart block (Case 3).



A. *B.*

Fig. 3.—Lead II. *A*, Before injection, P-R interval 0.44 second and heart rate 64 per minute; *B*, After injection of 450 mg., P-R 0.36 second and heart rate 84 per minute.

CASE 3.—This patient, a man aged 22 years, weighing 120 pounds, had infectious hepatitis. The P-R interval was 0.44 second and the heart rate was 68 per minute before the injection (Fig. 3). After injection of 200 mg. the P-R interval shortened to 0.36 second and the heart rate increased to 84 per minute. This then remained the same even when 450 mg. of the drug was injected. There were no general toxic symptoms and no premature beats appeared. The P-R interval returned to preinjection level within thirty minutes. Subsequently injection of atropine, 1/100 gr. intravenously, produced similar effects.

DISCUSSION

Culwell and associates[3] administered chloroquine hydrochloride intramuscularly in single doses of 2.5 to 5.5 mg. of the base per kilogram body weight in prison volunteers with experimental sporozoite-induced vivax malaria and found no evidence of toxicity. Virgil Scott[8] studied the toxicity and therapeutic efficacy of single intravenous injections of chloroquine in doses of 5.7 to 14.9 mg. of base per kilogram body weight in patients with falciparum malaria and found that the toxic effects appeared to be related principally to a depressor effect of the drug. With undiluted intravenous injections a fall in systolic and diastolic blood pressures averaging 26 and 9 mm. Hg, respectively, and an average increase of pulse rate by 6 beats per minute was observed. He noted that the depression of blood pressure was only of short duration, the pretreatment level being approximated within ten to thirty minutes. There is, however, no mention of any cardiac action of chloroquine.

Though there were no toxic effects in Case 3 with heart block, they were severe in both the cases of fibrillation, even though the maximum dose did not exceed 9 mg. per kilogram weight. The cardiac effects in both were identical. The first effect was slowing of auricular rate converting fibrillation to flutter, and then there was stimulation of ectopic impulse formation giving rise to ventricular premature beats isolated as well as in groups. The effects were only for a short duration. Ectopic beats disappeared within twenty minutes and flutter changed to flutter fibrillation or impure flutter. In another ten minutes the rhythm reverted back to fibrillation. It appears that the slowing of the auricular rate is probably due to an increase in the refractory period of the auricles, which was, however, not sufficiently great to reduce the rate still further and convert the flutter to sinus rhythm. This action of chloroquine resembles the vagolytic action of quinidine, but the latter has also a direct effect on the musculature which lengthens the refractory period and the vagolytic action enhances this effect. It seems that chloroquine did not have this direct effect on the musculature with the dosage employed. That the action is probably vagolytic in nature is supported by the effect seen in the third case. Chloroquine shortened P-R interval from 0.44 to 0.36 second and increased the cardiac rate from 68 to 84 per minute and an identical effect was produced by atropine. In this case also, the effects were of a short duration.

The above observations do not support the observations in animal experiments of Arora and associates[2] who found that chloroquine was more effective than quinidine in its antifibrillatory action. In animal experiments fagarine was also found to abolish instantly auricular flutter and fibrillation when given intravenously.[6] Fagarine even in large doses did not precipitate extrasystoles in dogs, but subsequently Scherf and associates,[7] who gave fagarine to thirteen patients with auricular flutter and fibrillation or paroxysmal tachycardia, found that six of these developed multifocal ventricular extrasystoles and, in two instances, ventricular fibrillation ensued. Experience with chloroquine in both the cases of fibrillation was similar to that of Scherf and associates[7] with fagarine. Multiple premature ventricular beats and short runs of paroxysmal ventricular tachycardia appeared in both, showing that chloroquine stimulated ectopic impulse formation in the ventricular musculature. This effect also resembles that of quinidine. Quinidine is known, sometimes, to precipitate ectopic beats or increase the number of those previously present, the majority of such observations being made in cases with auricular fibrillation as happened in our cases of fibrillation only. It seems that as in the case of fagarine the action of chloroquine in human beings is not the same as in animal experiments.

It is realized that this preliminary clinical trial is too small to arrive at definite conclusions. Though no toxic cardiac effects were observed in malarial patients,[3,8] the severe general toxic reactions and the stimulation of ectopic impulse formation in ventricles in both cases of fibrillation, have been considered worth reporting, so that they may be borne in mind in any further clinical trial of the drug in auricular arrhythmias. Chloroquine appears to be more toxic than quinidine, as the latter did not produce ectopic ventricular beats when administered subsequently to both the patients.

SUMMARY

Chloroquine given intravenously in two patients with auricular fibrillation produced identical cardiac effects. Fibrillation changed to flutter, but with further injection ventricular premature beats and short periods of ventricular tachycardia appeared.

Slowing of the auricular rate appears to be due to a vagolytic action of the drug similar to quinidine.

The effect of stimulation of ectopic impulse formation also resembles that noticed sometimes with quinidine, mainly in cases of auricular fibrillation.

I am thankful to Dr. L. R. Sarin, Superintendent, S.M.S. Hospital, for kind permission to publish these cases. My thanks are also due to Dr. S. N. Misra for recording the ECG tracings.

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ADDENDUM

Since writing this article, chloroquine was tried in one more case of auricular fibrillation. This patient, a woman aged 25 years, was admitted to the hospital for congestive cardiac failure with rheumatic mitral stenosis and regurgitation. Her cardiac failure was treated and at the time of the trial she was fully compensated and digitalized, auricular and ventricular rates being 400 and 72 per minute, respectively (Fig. 4), blood pressure 90/68 mm. Hg, and weight 70 pounds. Because of previous experience, the drug was injected more slowly at the rate of 1 c.c. per minute. Injection was started at 10:40 A.M. After injection of 240 mg. rhythm changed to auricular flutter with varying grade of A-V block, the auricular rate slowing to 300 while the ventricular rate increased to 106 per minute. After 300 mg. the ventricular rate became 123 and she complained of slight giddiness which, however, passed after five minutes. Then 60 mg. more was injected. Suddenly ventricular tachycardia and fibrillation ensued and the patient developed convulsions, became deeply cyanosed, and stopped breathing. Artificial respiration and oxygen were administered and procaine amide (Pronestyl) was immediately injected intravenously. Ten minutes later after 1 Gm. of Pronestyl, she started breathing, though labored, and the ECG showed some normal beats between periods of ventricular tachycardia. Even after 2 Gm. of Pronestyl in the course of 30 minutes, runs of tachycardia continued and the patient remained deeply unconscious. At 11:30 A.M. quinidine was slowly injected intravenously. After injection of 0.25 Gm. ECG tracings (Fig. 5) showed improvement (auricular flutter followed by smaller groups of ventricular premature beats). At this stage, again the patient developed convulsions, became blue, and respiration stopped. She was given 100 per cent oxygen with positive pressure. The ECG soon showed improvement which continued thereafter, and at 12:30 P.M. it showed only occasional premature beats. At 1:30 P.M. auricular fibrillation had returned and the patient moved her extremities for the first time and then became delirious. She regained complete consciousness at 6 P.M. and by next morning she felt all right except for slight general weakness.

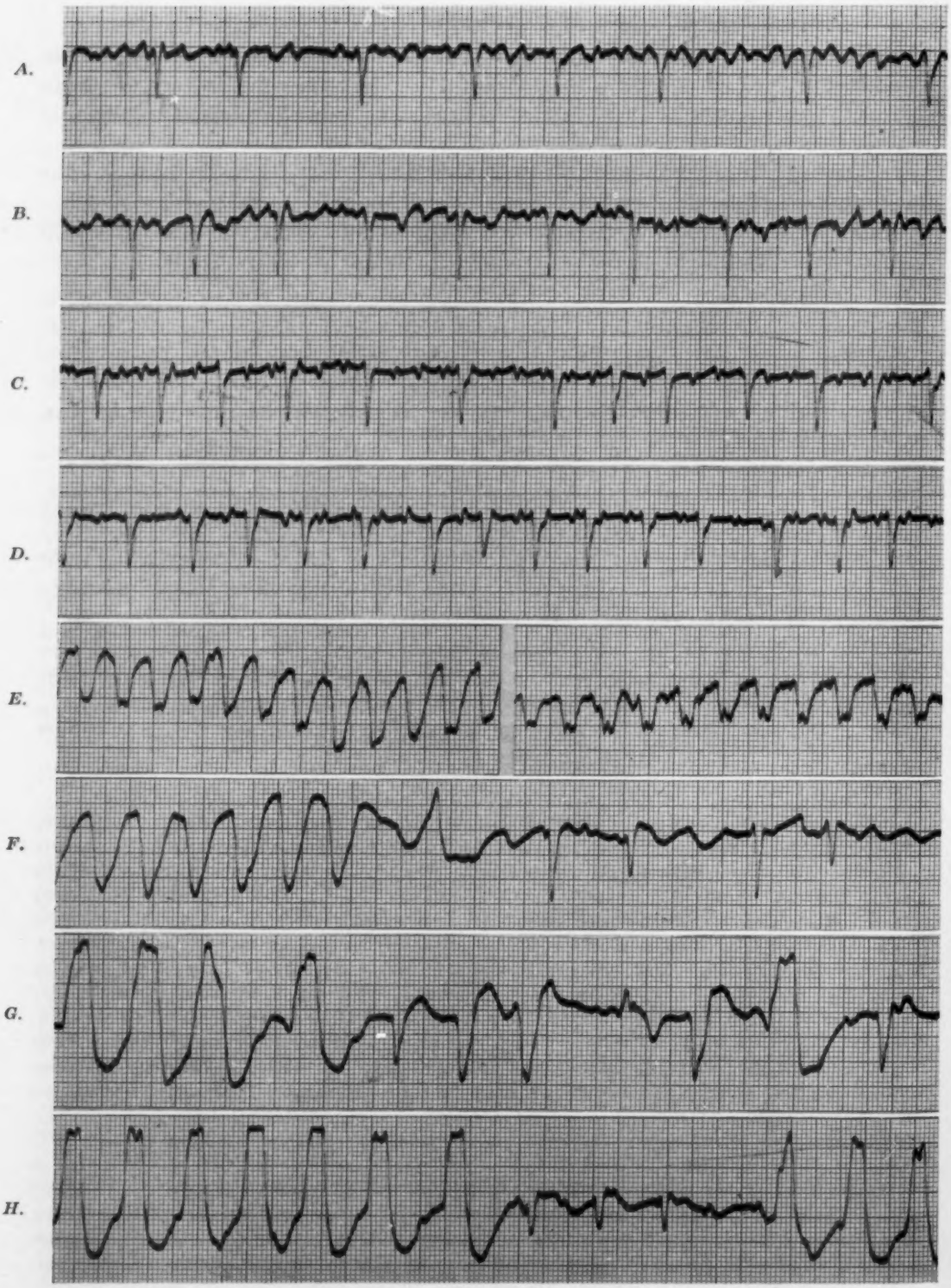

Fig. 4.—Lead V_1. *A*, Before injection; *B*, After 180 mg., impure flutter; *C* and *D*, After 240 and 300 mg., respectively, flutter with increased ventricular rate; *E*, After 360 mg., ventricular tachycardia; *F* and *G*, After Pronestyl; *H*, After 2 Gm. Pronestyl.

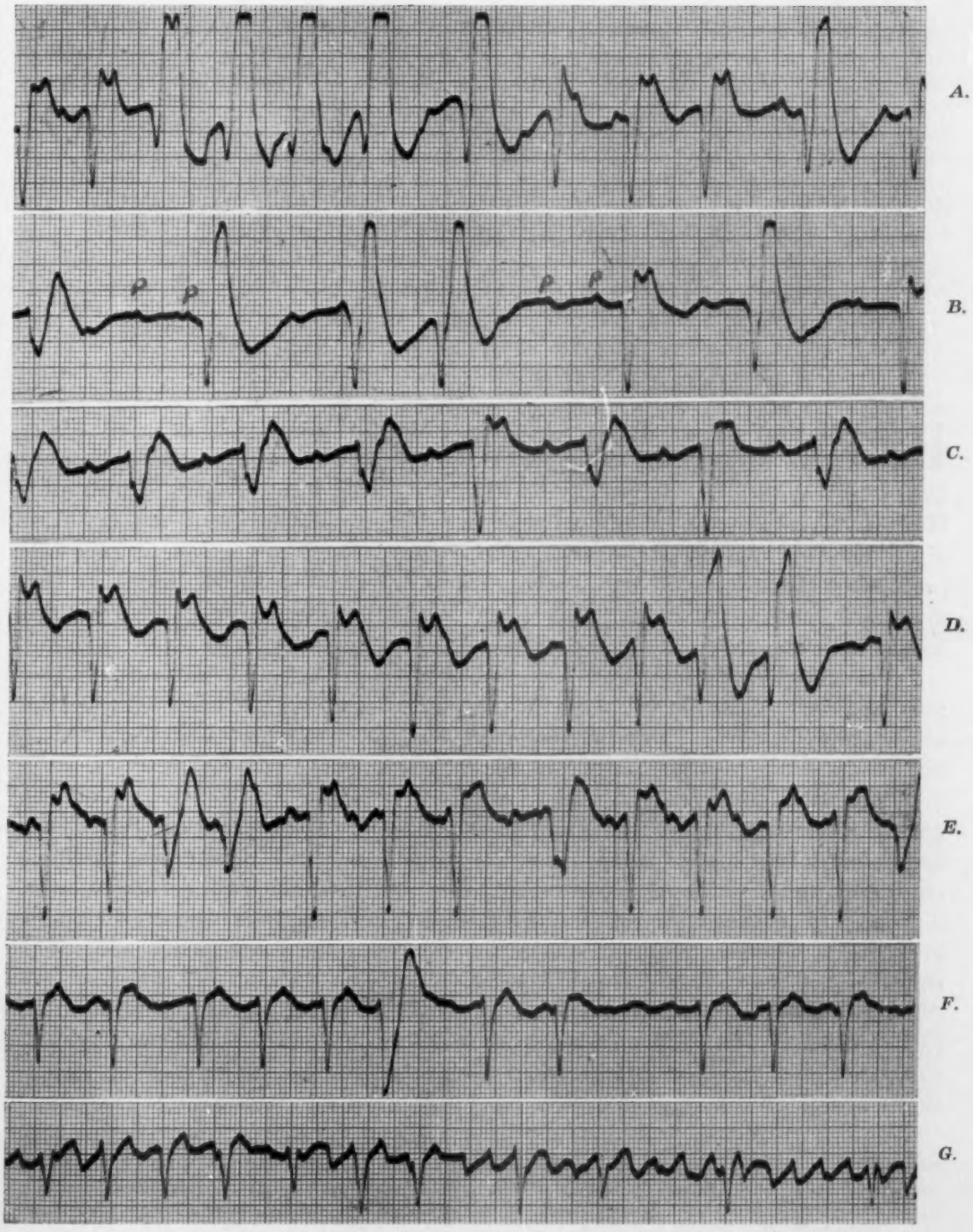

Fig. 5.—Lead V_1. *A*, After quinidine 0.15 Gm.; *B*, After 0.25 Gm., flutter and ventricular premature beats; *C* to *F*, Lessening of premature beats; *G*, Return to fibrillation.

This case developed most serious toxic manifestations of chloroquine, giving rise to ventricular tachycardia and fibrillation, Stokes-Adams seizure, and respiratory arrest. It was with the greatest difficulty that she could be revived, after 2 Gm. of Pronestyl followed by 0.25 Gm. of quinidine intravenously, and continuous oxygen inhalation with positive pressure. The drug apparently is too toxic in patients with auricular fibrillation and further trial has been abandoned.

PULMONARY ARTERIOVENOUS FISTULA LOCATED BY INDICATOR DILUTION STUDIES

JOHN A. CALLAHAN, M.D.,* H. FREDERIC HELMHOLZ, JR., M.D.,** AND JOHN W. KIRKLIN, M.D.***

ROCHESTER, MINN.

PULMONARY arteriovenous fistulas are said to occur uncommonly.[1] The first known description was made at necropsy, and a report was published in 1918 by Wilkens.[2] The diagnosis was first made during life by Smith and Horton.[3] Hepburn and Dauphinee[4] reported the first successful surgical removal of an arteriovenous fistula in 1940. Since that time, an increasing number of cases have been reported.[5,6] Burchell and Clagett[7] and others[8,9] discussed the syndrome and compared the hemodynamics of a pulmonary arteriovenous fistula with those of a peripheral arteriovenous fistula.

Vascular lesions associated with pulmonary arteriovenous fistulas may be seen in a roentgenogram of the thorax and may sometimes be demonstrated by angiocardiography.[1,10] Muri[5] recommended angiocardiography before operation because possible multiple lesions might otherwise escape detection.

Maier and his associates[10] reported a case in which the patient had undergone cardiac catheterization. The only abnormality they found was peripheral arterial unsaturation. Friedlich and co-workers[9] reported four cases in which cardiac catheterization was used. In three of these, the cardiac output was normal, and in one it was increased. Denolin and associates[11] reported that in one case in which cardiac catheterization was used the calculated venoarterial shunt was 50 per cent of systemic flow.

Two cases are presented which were studied before operation by cardiac catheterization. In each of these cases the location of the venoarterial shunt through the pulmonary arteriovenous fistula, as well as the absence of such a shunt in the other lung, was demonstrated by arterial indicator dilution studies.

CLINICAL DATA

CASE 1.—A 48-year-old farmer came to the Mayo Clinic in December, 1953, because of "lung trouble." One month previously a roentgenogram of his thorax had been made in a mobile unit. Shortly thereafter he had been advised to have further investigation. This was the first time a roentgenogram of his thorax had ever been made.

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*Assistant to the Staff, Mayo Clinic and the Mayo Foundation, Rochester, Minn., a part of the Graduate School of the University of Minnesota.

**Section of Physiology, Mayo Clinic and Mayo Foundation.

***Section of Surgery, Mayo Clinic and Mayo Foundation.

He said that exertion had always seemed to bother him more than it did his friends, but not enough to interfere with his work. He had had clubbing of the fingers as long as he could remember, and stated that his father's fingers looked just the same. He had not been aware of any cyanosis.

During physical examination, the blood pressure was found to be 112 mm. Hg systolic and 68 mm. diastolic and the heart rate was 80 beats per minute. The nail beds and lips appeared somewhat dusky and clubbing of the fingers was noted. Other physical findings were not significant.

The results of laboratory studies showed a concentration of hemoglobin of 18.2 Gm. per 100 c.c.; 5,470,000 erythrocytes and 6,300 leukocytes per c. mm. of blood, and a normal differential count. Results of tuberculin skin tests were negative. Examinations of the sputum for malignant cells and acid-fast bacilli gave negative results.

Fig. 1.—(Case 1.) The lesion is visible in the right mid-lung field.

A roentgenogram of the thorax (Fig. 1) showed a sharply circumscribed mass, 2.5 cm. in diameter, anterior and lateral to the right hilus. A smaller, lobulated mass was seen close to the first mass. Between these two masses a small calcified region was evident. Tomograms revealed that the mass was made up of many nodules ranging from 3 to 3.5 mm. in diameter. These nodules appeared to be in the right middle lobe near the horizontal fissure. Evidence of cavitation was absent. The middle lobe bronchus appeared to be somewhat compressed at its point of origin. Because of this, bronchoscopic examination was done. Results were negative.

CASE 2.—A 51-year-old married woman was first seen at the clinic in December, 1954. She had been examined elsewhere four years prior to this because of chronic fatigue. Cyanosis, clubbing of the fingers, and polycythemia were noted at that time. She was advised to take digitalis and to reduce her activity. Two months prior to registration in December, 1954, after an upper respiratory infection, cough and night sweats developed. One month prior to registration, she slowly "blacked out" while sitting in a chair and awoke on the floor, unable to see. Vision gradually returned during the next hour. Two weeks prior to registration she fainted, was unconscious for three or four minutes and recovered without apparent sequelae. Careful questioning during examination revealed that cyanosis and clubbing had been present since childhood.

On physical examination, the blood pressure was found to be 104 mm. Hg systolic and 68 mm. diastolic and the heart rate, 78 beats per minute. Slight cyanosis of lips and fingers was observed,

which was increased by exertion. Clubbing of the fingers was moderate. A systolic bruit was heard on the right upper part of the thorax during inspiration. Neurologic or visual abnormalities were not found.

Laboratory studies gave the following results: concentration of hemoglobin, 17.1 Gm. per 100 c.c. of blood; 4,880,000 erythrocytes and 6,500 leukocytes per c. mm. of blood. The volume of packed red cells was 62 per cent.

A roentgenogram of the thorax (Fig. 2) revealed an oval shadow, 4 by 6 cm., in the right upper lung field with two broad shadows leading from it to the right hilus. Fluoroscopy demonstrated pulsation of the shadow.

Fig. 2.—(Case 2.) The lesion is visible in the right upper lung field.

LABORATORY METHODS AND RESULTS

Cardiac catheterization was carried out by means of methods described elsewhere.[12] The oxygen saturation of the blood was determined both by manometric[13] and by photoelectric techniques.[14] Arterial dilution curves of T-1824 were used for localization of vascular shunts.[15]

The results of cardiac catheterization are summarized in Table I. The findings in the two patients are essentially similar. Intracardiac and intravascular pressures were normal. The values for oxygen saturation of peripheral arterial blood were found to be below normal, while the patients were at rest, breathing air. The arterial blood was not fully saturated with oxygen when the patients breathed oxygen. The oxygen capacity of the blood was elevated. The cardiac output was normal. The venoarterial shunt, calculated from data on oxygen saturation of the blood, was 32 per cent of systemic flow in Case 1 and 53 per cent of systemic flow in Case 2, while the patients were at rest, breathing air.

In both cases arterial indicator-dilution curves were recorded after injection of T-1824 at multiple sites. Dilution curves recorded in Case 1 are reproduced in Fig. 3. The dilution curves recorded after injection of dye into the left pulmonary artery and into the right pulmonary artery beyond the lesion were normal. Those recorded after injection of dye into the superior vena cava and the right pulmonary artery proximal to the lesion had short appearance times and abnormal deflections indicative of a venoarterial shunt.

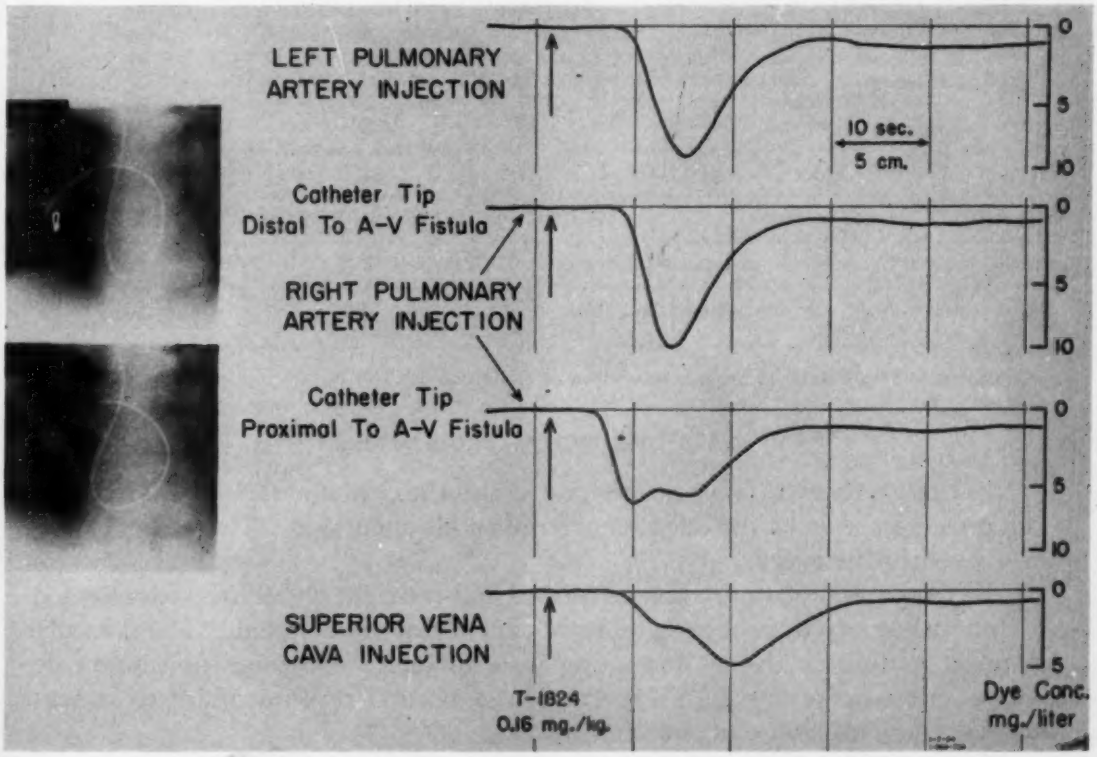

Fig. 3.—Demonstration of pulmonary arteriovenous shunt by arterial indicator-dilution curves of T-1824 recorded in Case 1. The top two dilution curves are normal. The first was recorded after injection of dye into the left pulmonary artery. The second and third were recorded after injection into the right pulmonary artery, distal to and proximal to the lesion. The positions of the cathteer are demonstrated in the x-ray inserts. The third and fourth dilution curves have short appearance times and abnormal initial deflections characteristic of "venoarterial" shunts.

In Case 2, the dilution curve recorded after injection of dye into the left pulmonary artery was normal. Those recorded after injection of dye into the right pulmonary artery and superior vena cava had short appearance times and abnormal initial deflections, indicative of a venoarterial shunt.

The dilution curves of particular interest are those recorded after injection of dye into the pulmonary arteries. In Case 1, it was possible to make an injection of dye beyond the lesion and demonstrate that there was no shunt beyond that point. In both cases, it was possible to demonstrate that there were no significant lesions in the opposite lung.

TABLE I. RESULTS OF CARDIAC CATHETERIZATION

	CASE 1	CASE 2
Pressure, mm. of mercury		
Right atrium	4/1	4/0
Right ventricle	25/3	13/2
Pulmonary artery	21/9	12/5
Radial artery	98/60	90/57
Oxygen saturation of blood, per cent		
Patient breathing air		
Pulmonary artery	68	66
Radial artery	90	81
Patient breathing oxygen		
Pulmonary artery	79	75
Radial artery	99	93
Oxygen capacity of blood, c. c. per 100 c. c.	21.9	23.0
Surface area, square meters	1.76	1.62
Cardiac index, liters per minute per square meter	2.7	3.5
Right-to-left* shunt, per cent of systemic flow	32	53

*Calculated from data on oxygen saturation of blood.

DATA ON SURGICAL PROCEDURES

In Case 1, thoracotomy was performed and the right middle lobe was resected. The resected specimen included an arteriovenous aneurysm. The patient made an uneventful recovery.

In Case 2, thoracotomy was performed and the right upper lobe was resected. A thin-walled arteriovenous fistula and aneurysm were found. The vascular channels leading to the malformation were dilated. Auricular fibrillation developed after operation. This reverted to a normal rhythm under treatment. Recovery was otherwise uneventful.

SUMMARY

Two cases of pulmonary arteriovenous fistula are described in which thoracotomy was performed and the lesion resected. In both patients the site of the venoarterial shunt and the absence of significant lesions in the opposite lung were demonstrated by indicator-dilution curves. During cardiac catheterization, peripheral arterial unsaturation was demonstrated and venoarterial shunts of 32 per cent of systemic flow and 53 per cent of systemic flow, respectively, were calculated.

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ESOPHAGEAL ULCER ERODING INTO THE LEFT VENTRICLE WITH FATAL HEMORRHAGE

WILLIAM H. CONKLIN, M.D.

ALBANY, N. Y.

A REVIEW of the literature fails to reveal a reported case of an esophageal ulcer eroding the left ventricular myocardium, with resultant fatal hemorrhage. There have been numerous reported cases[1-4] of esophagoaortic communications with fatal hemorrhage, but these have been secondary to infection, foreign body perforation, or surgical procedures. In the various accounts of esophageal ulcer consulted,[4-12] no mention of involvement of the heart was made. There have been, however, eight reported cases of gastric peptic ulcer eroding the left ventricular myocardium, with resultant exsanguination. The first case was reported by Oser and Chiari, in 1880,[13] and the latest by Erhardt, in 1933.[13] Other reported cases include Finny, in 1886,[14] Fenwick, in 1897,[15] and Tylecote, in 1913.[16]

CASE REPORT

E.K., a 64-year-old white married woman, was admitted to St. Mary's Hospital for the twelfth time on June 13, 1954, with the complaints of burning epigastric pain radiating to an operative scar on the left chest and shortness of breath. The burning sensation had been intermittently present from her first admission 23 years before, and present constantly during the previous four years. On her first admission, aside from this sensation, review of systems disclosed fatty food intolerance. Physical examination and laboratory studies were within normal limits, but x-ray examination of the gall bladder revealed it to be "small, poorly functioning, and containing a radioopaque stone." Her symptoms were controlled with antispasmotics and a low fat diet. Two months later she was readmitted with history, physical findings, and laboratory evidence compatible with acute cholecystitis. At cholecystectomy the findings of acute and chronic cholecystitis with cholelithiasis were noted. The patient had an uneventful recovery and was symptom free on discharge. One month, and again nine months postoperatively, she was readmitted with epigastric burning, followed by nausea and then vomiting of small amounts of mucoid material, and accompanied by "difficulty in getting her breath." Abnormal findings consisted of tenderness in the operative scar and slight angulation and little loss of mobility of the second portion of the duodenum seen on upper gastrointestinal series. Symptomatic treatment readily controlled the symptoms, and the patient was felt to benefit most from reassurance.

In 1950, 19 years later, she re-entered the hospital with the complaint of vomiting small amounts of mucoid material after meals for 17 years. Physical examination and laboratory studies were within normal limits. An electrocardiogram was interpreted as showing left axis deviation. Barium enema exhibited diverticuli in the sigmoid colon, and a supradiaphragmatic, midline density compatible with a hiatus hernia. Barium swallow revealed esophageal dilatation due to extreme cardiospasm. Antispasmotics and dietary measures produced no relief, and an esophagogastroplasty was performed. At operation the heart, lungs, and great vessels were

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normal. The esophagus was markedly constricted at the cardia, with moderate proximal dilatation. Again the postoperative course was uneventful, the patient being discharged on the tenth postoperative day on a soft diet.

Two years later the patient was admitted with complaints of numbness of the left side of the face and steady, burning pain in the left epigastrium and chest over the operative scar. Physical examination revealed a weight loss of 15 pounds since 1950, and a blood pressure of 180/120 mm. Hg. A hemogram showed a normocytic, hypochromic anemia, with normal white cell count and differential. Occult blood was present in two stool specimens. The urinalysis, serum electrolytes, urea nitrogen, serum proteins, and ACTH tests were normal. Upper gastrointestinal stud-

Fig. 1.—Two tiny flecks of barium may be seen at the tip of the arrow, with the outline of the markedly dilated esophagus above.

ies demonstrated a marked dilatation of the lower esophagus, forming a blind pouch, but a normal intact mucous membrane throughout. Diagnostic novocain block of the third portion of the trigeminal nerve did not affect the facial sensation. She responded slowly to analgesics, special diet, and multivitamin therapy.

One month later the patient was readmitted with the same complaints. There were no changes in physical examination. The hemogram again demonstrated a normocytic, hypochromic anemia. Repeat laboratory studies including serum amylase, serum calcium and phos-

phorous, and alkaline phosphotase determinations were within normal limits. The urine was negative for porphyrins. A lumbar puncture showed normal cerebrospinal fluid, and examination of a bone marrow aspirate revealed no abnormality. Stools continued to show occult blood. Skeletal x-rays revealed only minimal osteoporosis. Repeat gastrointestinal series showed some delay in passage of barium at the cardia and marked thickening of the gastric mucosa. Response to therapy was again slow.

Six months later the patient entered the hospital with complaints of pain, redness, swelling, and limited motion of the fingers and wrists. There was no change in the facial numbness, epigastric burning, or pain in the thoracotomy scar. Physical examination revealed a blood pressure of 200/100 mm. Hg. The distal and middle phalanges of the fingers of both hands were red, warm, slightly enlarged, tender on palpation, with some limitation of motion. No other joints were abnormal. All laboratory examinations were within normal limits except for an elevated sedimentation rate of 32 mm. per hour. The patient was treated with cortisone, butazolidin, and protamide with good response.

Five weeks later she returned with complaints of epigastric burning, vomiting, pain in the left side of the face, and increasing weakness. Physical examination revealed slight deformity of the fingers and tenderness of the operative scar on palpation. The laboratory findings were a hypochromic anemia, reticulocyte count 20 per cent, and sedimentation rate of 24 mm. per hour. Platelet count, bleeding and clotting times, urinalysis, urea nitrogen, and serum protein determinations were again within normal limits. Repeat upper gastrointestinal examination demonstrated a normal mucosa with no evidence of inflammation or ulceration. Barium enema showed diverticuli in the sigmoid colon. Treatment with whole blood, sedatives, analgesics, and antispasmotics produced relief of symptoms.

The eleventh admission was three months later, when complaints of vomiting black fluid, epigastric burning, and ankle swelling were elicited. Physical examination showed distended neck veins with normal direction of flow and cardiomegaly with an associated Grade 3 apical systolic murmur. Fine, moist râles were heard over both lower lung fields posteriorly, and there was three-plus pitting, pretibial edema. On admission the hemoglobin was 3.7 Gm., and the hematocrit was 15. The patient was digitalized, given supplementary oxygen, and 1,000 c.c. of whole blood was administered. An electrocardiogram showed low voltage. The stools were again positive for occult blood. Urinalysis, serum proteins, serum amylase and lipase, cephalin flocculation, and a vitamin A tolerance test were within normal limits. X-ray studies revealed an irregularity suspicious of ulceration at the esophagogastric junction (see Fig. 1). Esophagoscopy revealed esophagitis with an ulcerated area on the anterior wall at the junction with the cardia. Pathologic examination of a biopsy of this lesion revealed only chronic inflammation. Further transfusions, antispasmotics, an ulcer diet with between-meal feedings, antacids, and sedation produced slow improvement.

Two months later, on her final admission, the pain, shortness of breath, and ankle swelling had not been controlled at home despite continuation of therapy. The blood pressure was 170/100 mm. Hg. There was dullness on percussion of both lung bases posteriorly, with numerous fine, moist râles in this region. There was cardiomegaly, with a Grade 2 apical systolic murmur. The liver edge was palpable 3 cm. below the right costal margin, and there was two-plus pitting, pretibial edema. The hemogram showed a normocytic, hypochromic anemia, and an elevated sedimentation rate. A bone marrow aspirate demonstrated erythrocytic hyperplasia. The urine contained two-plus albumin, and the stools were positive for occult blood. An electrocardiogram was interpreted as showing changes "suggestive of old posterior infarction." On the second hospital day the patient developed acute pulmonary edema which responded satisfactorily to the use of rotating tourniquets and oxygen. Repeat electrocardiogram showed "diffuse myocardial damage." Chest x-ray revealed cardiac enlargement, pulmonary congestion, and minimal bilateral hydrothorax. Serial electrocardiograms demonstrated progressive changes compatible with the healing phases of myocardial infarction. On the thirty-fifth hospital day the patient vomited about 200 c.c. of dark brown bloody fluid, and passed several tarry stools, without change in the hematocrit. Following this, she seemingly improved. She had less pain, better appetite, and no further hematemesis or melena, and was ambulated to a chair without distress. On the fifty-seventh day, shortly after the noon meal, the patient suddenly vomited about 500 c.c. of

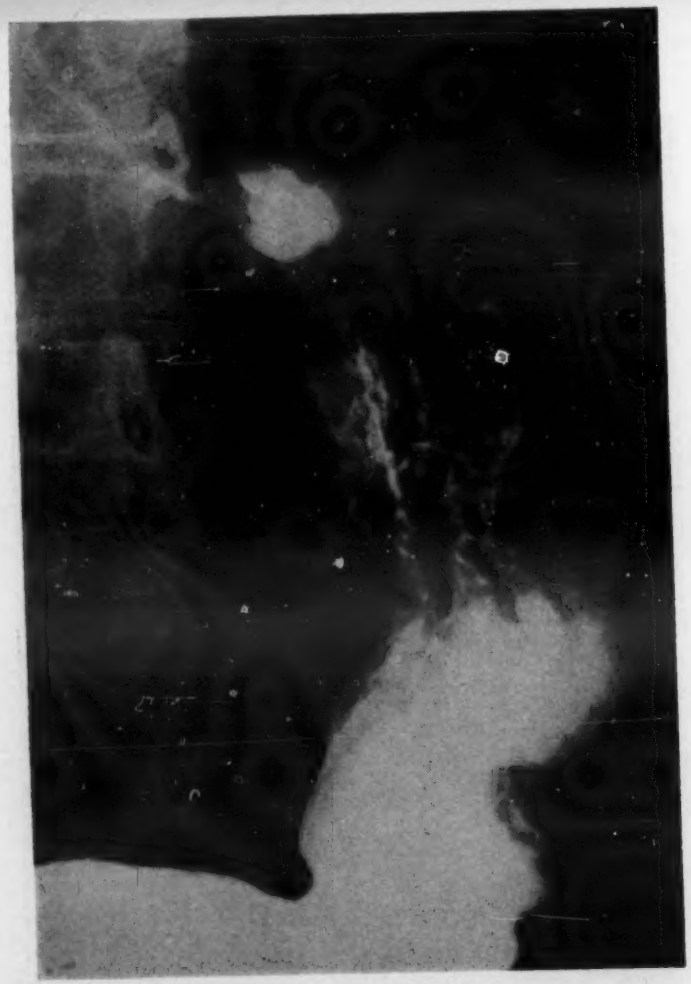

Fig. 2.

Fig. 3.

Fig. 2.—Residual barium in the region of the ulcer crater after barium swallows.

Fig. 3.—The esophagus and stomach opened posteriorly showing the ulcerated area and the blood still adherent to the gastric mucosa. The arrow indicates the base of the ulcer.

Fig. 4.

Fig. 5.

Fig. 4.—The arrow indicates the perforation into the left ventricular cavity, and the fibrinous exudate surrounding it.
Fig. 5.—Low power view demonstrating the sinus tract through the myocardium.

coffee-ground material, passed a large tarry stool, and lapsed into shock. Massive transfusions stabilized her blood pressure and pulse after about six hours, and although she continued to regurgitate small amounts of coffee-ground material during the next twenty-four hours, it was felt the active bleeding had ceased. Approximately seventy-two hours later the patient again had massive hematemesis and melena, and went into irreversible shock despite massive transfusions and norepinephrine. The patient expired about nine hours after the onset of this episode.

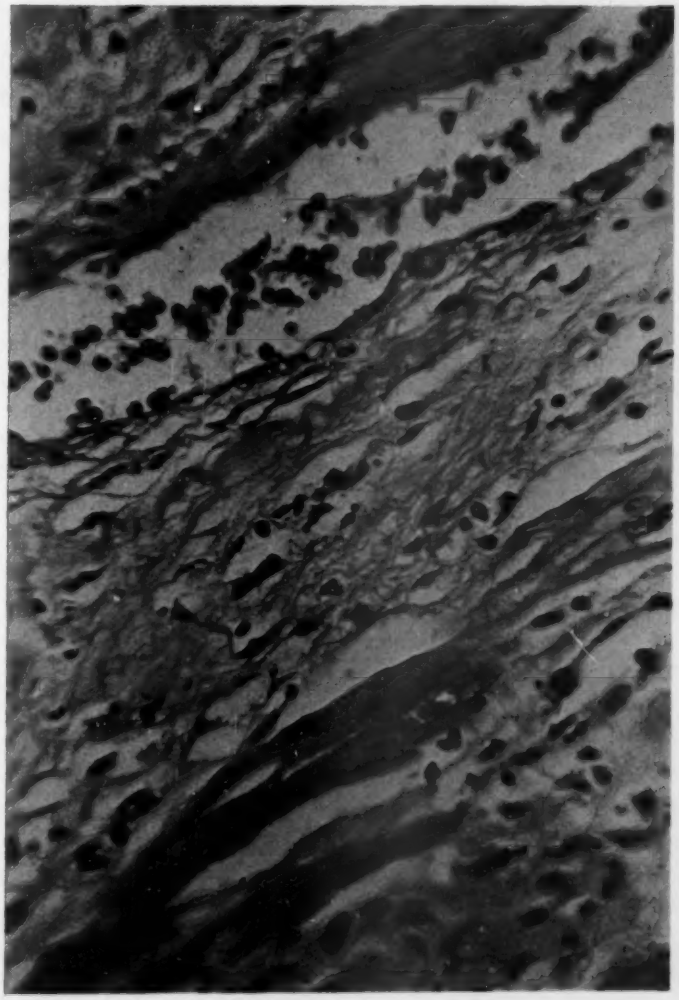

Fig. 6.—High power view showing the tract containing blood and the surrounding tissue.

Necropsy examination revealed the presence of dense adhesions binding the anterior wall of the distal one-third of the esophagus to the posterolateral wall of the left ventricle (see Figs. 2 and 3). There was a fistulous tract connecting the cavity of the left ventricle with the base of the esophageal ulcer (see Figs. 4 and 5). There was evidence of an old anterior myocardial infarction, and the gastrointestinal tract was filled with old blood.

SUMMARY

A case of esophageal ulcer eroding into the cavity of the left ventricle, with resulting exsanguinating hemorrhage into the gastrointestinal tract is reported. A review of the literature fails to disclose a previous report of this entity.

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CONGENITAL CYANOTIC HEART DISEASE IN ONE OF MONOZYGOTIC TWINS

OTAVIO DE OLIVEIRA PAES, M.D.*

RIO DE JANEIRO, BRAZIL

IDENTICAL twins, as they provide material for the study of individuals with the same hereditary background, have often been utilized for the evaluation of the role of heredity and environment in health and disease.

For a long time there has been the belief that a congenital malformation in a similar twin should be necessarily shared by his partner. This idea was defended by Mc Farlane and Meade,[1] who through an extensive review of the literature were not able to find a case of a definite malformation affecting only one of monozygotic twins. The absence of marked differences and the strikingly similar physical and mental behavior presented by this class of twins in health and disease (a number of examples can be found in the paper by Murray[2]) is to be expected, since they are genetically one and the same individual.

The work of Macklin[3] brought more evidence favoring this concept. She studied seventy-two sets of twins with malformations, and found that in the group in which both twins were malformed the majority was of like-sexed, probably monozygotic pairs.

This way of thinking has been modified. Kindred's[4] careful analysis of twin pregnancies with one twin blighted showed that this occurs with the same frequency among homologous and heterologous twins. Blighting occurred usually between the third and fifth months. These homologous malformed fetuses can thus well represent instances of pure environmental factors acting selectively upon one embryo, sacrificed early in the competition for life. Morison[5] reports two other sets of twin births. In both instances they were identical and one of them grossly malformed. The partners were well formed. He suggests a mechanism for the production of these abnormalities based on a disturbance of production of some essential substance, which would affect developing structures at critical points.

At present there seems to be little doubt that, although it occurs rarely, intrauterine conditions can modify a genotypic pattern or permit the expression of a pathologic gene.

Cardiac malformations are seldom reported as occurring in only one of monozygotic twins. As far as we know, Dubreuil-Chambardel[6] reported a classical case of dextrocardia. Two instances of patent ductus arteriosus were published, one by Mc Clintok[7] and another by Wade,[8] who added a case of pulmonary stenosis; and a case of auricular septal defect was observed by Forsyth and Uchida.[9]

From the II. Medizinischen Universitätsklinik (Professor Dr. K. Fellinger), Vienna, Austria.
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*Present address: Joinville, Santa Catarina, Brazil.

The case of dextrocardia described by Dubreuil-Chambardel does not represent a valid difference between twins. They had signs of mirror symmetry, as transposition also of abdominal viscerae and cleft lip, one in the right, the other in the left lip. Mirror symmetry is a phenomenon generally presented by double monsters and is determined at the time of division of the egg. As for patent ductus arteriosus, it can hardly be considered a malformation when it occurs as an isolated defect. There is completed development of the heart and great vessels, and no embryologic arrest. Its closure is conditioned by complex physiologic processes, as shown by Kennedy,[10] and the cause of patency at abnormal ages must be found in the failure of one or more of these mechanisms rather than in a true malformation.

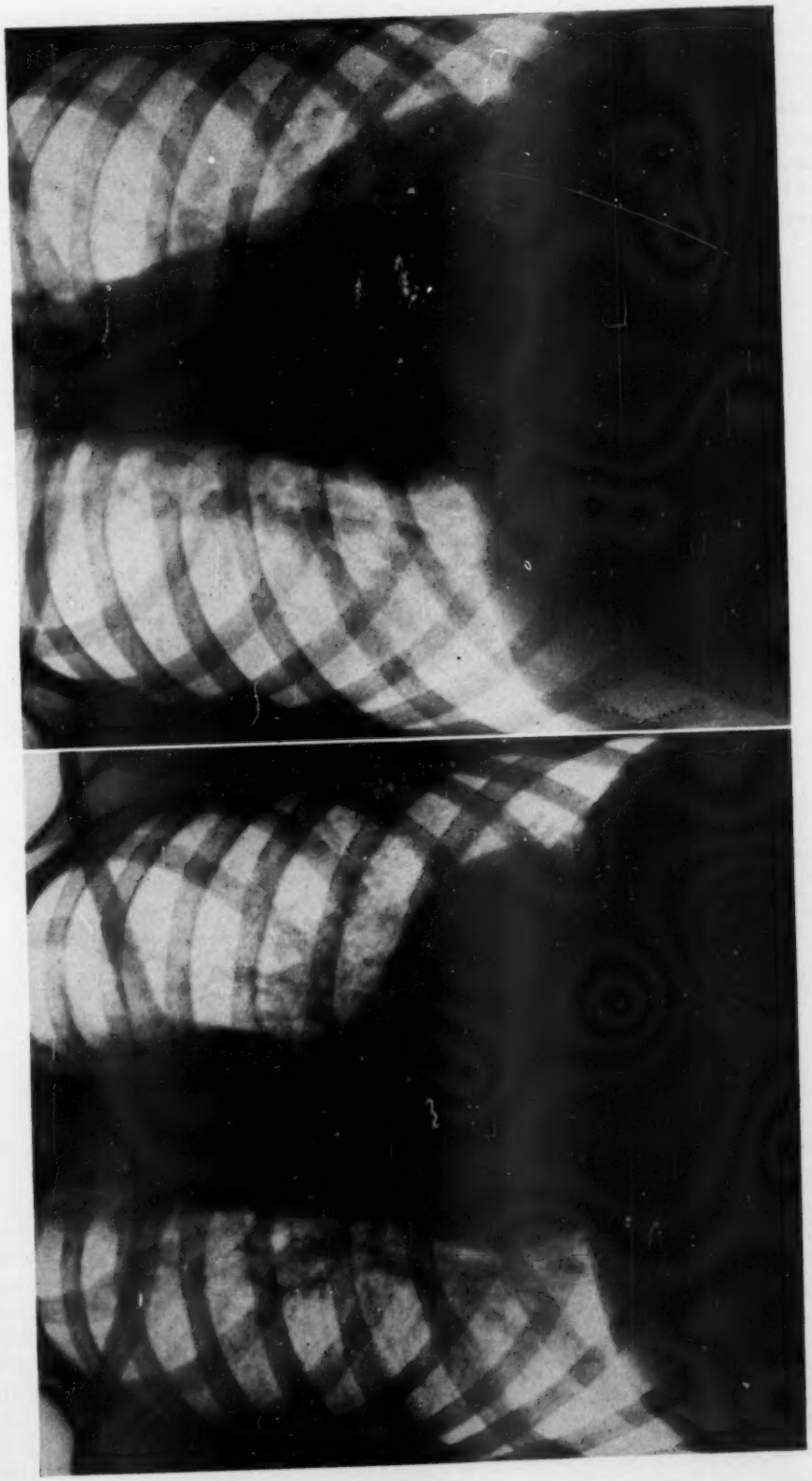
Thus when we want to study cardiac malformations which are developed in uterus in only one of a pair of similar twins, we are left with those of Forsyth and Uchida and the pulmonary stenosis reported by Wade. We want to report the following case.

Fig. 1.—The twin sisters, Regina and Cornelia W.

CASE REPORT

Regina and Cornelia W., 4-year, 11-month-old white twin sisters, were brought to the hospital for cardiac examination. Regina had cyanosis and clubbing of fingers and toes. Cornelia was normal.

They were of the same appearance and very much alike (Fig. 1), Regina being a little thinner than her sister. At birth she weighed two hundred and fifty grams less. The color of their eyes and hair was identical. From the obstetrical report (St. Joseph Krankenhaus Hacking, Vienna, Geburtshilfe Abteilung Journal, number 2.209) the delivery was normal. There was only one placenta. The twins were classified as monozygotic, but further details and histologic examination of the membranae were not recorded. The mother was 39 years old and had been well throughout pregnancy. She has had four other children. Three are in good health and one died of scarlet fever. There were no cases of congenital heart disease in the family. The twins had a normal development, walking and speaking at expected ages, and both had an alert disposition.



A. *B.*

Fig. 2.—*A*, Regina W. Typical "coeur en sabot." Signs of abnormal pulmonary vascularization. *B*, Cornelia W. Normal heart.

Regina was not cyanotic at birth. At 3 weeks of age difficult respiration was noticed. The family physician believed it to be pneumonia, but did not observe any alteration of color. Cyanosis was first seen at 6 weeks of age, being slight at rest and marked on exertion. Despite this she was able to play with other children, but required frequent stops for rest. Recurrent febrile sore throats caused periodic embarrassment of the circulatory condition with attacks of dyspnea, but only once was she seen to squat.

Physical examination disclosed a well-developed, slightly dyspneic girl. There was marked cyanosis and clubbing of fingers and toes. A thoracic deformity with bulging of the midsternal region was present. The point of maximal impulse was not visible and could hardly be felt below the nipple. There was no thrill. On auscultation the second sound was accentuated in the pulmonic area. Reduplication could not be elicited either by exertion or on deep respiration. The

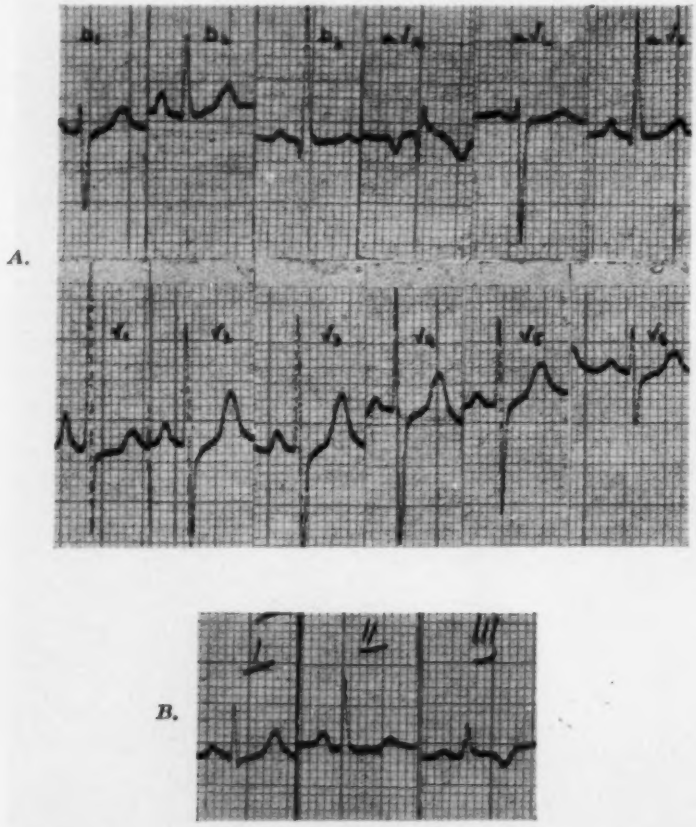


Fig. 3.—*A*, ECG Regina W. Right axis deviation and right ventricular hypertrophy. *B*, ECG Cornelia W. Normal tracing.

first mitral sound was of good quality. A soft continuous murmur was heard strictly localized in the left infraclavicular and axillar areas. The radial pulse was weak. The lungs were normal and the liver was palpated at two fingerbreadths below the costal margin and did not pulsate.

Fluoroscopic examination: The heart was slightly enlarged. The right ventricle seemed enlarged. There was a hollow at the area of the pulmonary conus. The lung fields showed diminished vascularization, the right lung seeming to be more vascularized than the left. The hili, especially the left, were of abnormal shape and did not show any definite relation with the cardiac border. The aortic shadow was enlarged and the aortic knob conspicuous (Fig. 2,*A*). In the left oblique position the pulmonary window was clear.

Conventional electrocardiogram showed right axis deviation and right ventricular hypertrophy (Fig. 3,*A*).

Fig. 4.

Fig. 5.

Fig. 4.—Regina W. Angiocardiogram at approximately 2 inches. Superior vena cava, right auricle, right ventricle, and dextroposed aorta well filled. The pulmonary artery is not visible.

Fig. 5.—Regina W. Angiocardiogram at approximately 4 inches. There is some contrast in the pulmonary vessels.

Angiocardiography was performed. A dextroposed aorta filled well at approximately 2 seconds (Fig. 4). The pulmonary trunk and its principal branches could not be seen. At 4 seconds some contrast appeared in the pulmonary vessels, and its concentration did not increase (Fig. 5).

The final clinical diagnosis was pseudotruncus arteriosus, with collateral circulation to the lungs. Operation was not indicated.

Physical examination, fluoroscopy, and a 12-lead electrocardiogram did not disclose any abnormality in Cornelia.

These cases are highly interesting because they are surely not of genetic origin, and cannot be explained by any mechanisms other than those causing the defect in babies with no known pathologic heredity. Also no illness which might have affected the embryo occurred in the mother during the pregnancy. More complete knowledge of the chemical-metabolic exchanges at the time of cardiovascular development could throw light on this problem.

SUMMARY

After a review of the literature a case of congenital cyanotic heart disease occurring in one of monozygotic twins is reported.

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THE ASSOCIATION OF ADAMS-STOKES ATTACKS AND CHEYNE-STOKES RESPIRATION

EDWARD J. MEARS, M.D.*

AMARILLO, TEX.

THE association of Adams-Stokes attacks and Cheyne-Stokes respiration has been reported a few times in the past. As early as 1912 Bäumler[1] cited a case of congestive heart failure with Cheyne-Stokes respiration; during the height of the ventilatory period on several occasions he noted a complete cessation of ventricular activity.

A review of the indices of several textbooks and monographs on cardiology and internal medicine failed to disclose any reference to Adams-Stokes attacks produced by Cheyne-Stokes respiration. This report again calls attention to this association, and summarizes the available information concerning its mechanism.

CASE REPORT

A 57-year-old man was admitted complaining of midepigastric and low substernal pain of one week's duration. There was occasional associated dyspnea and several episodes of nausea and vomiting. A few days after the onset of these symptoms and prior to admission he noted several questionably tarry stools. He denied any radiation of the pain but felt it was definitely aggravated by eating as well as exertion and was relieved by rest. He also had anorexia and mild intermittent dizziness but noted no ankle edema or orthopnea.

Physical Examination.—The blood pressure was 120/80 mm. Hg, the pulse regular at 38 per minute. He was moderately lethargic and appeared chronically ill but did not seem to be in any acute distress. There was moderate conjunctival pallor. The heart sounds were very distant with an apical rate of 38. No significant murmurs were heard; a "bruit de cannon" was not detected. The lung fields were clear throughout. There was moderate epigastric tenderness and spasm. The liver edge was palpated 3 cm. below the right costal margin and was moderately tender. No other abdominal organs or masses were palpable. There was no peripheral edema. There was no tarry stool on the rectal glove.

Laboratory Data.—W. B. C. 10,600 with a normal differential. The hemoglobin was 15.5 grams and the hematocrit 36 per cent. The sedimentation rate was 27 mm. in the first hour. The urine showed 1 + albumin, 6 to 8 white blood cells per high power field, and many coarsely granular casts. The nonprotein nitrogen was 57 mg. per cent, prothrombin time 19 seconds (31.5 per cent), carbon dioxide 24.5 meq./L., and serum chloride 98 meq./L. The serologic tests for syphilis were negative. The electrocardiogram on admission (Fig. 1) showed complete heart block and was compatible with acute anteroseptal myocardial ischemia.

He was treated by absolute bed rest, sedatives, meperidine, and slow digitalization. Several hours following admission he developed intermittent episodes of dizziness, quivering of both hands, and bizarre movements of both eyes. His blood pressure dropped to 70/40 mm. Hg while the pulse remained at 38. Atropine, 0.4 mg., q 4 h, and nasal oxygen were begun and 1,000 ml.

From the Veterans Administration Hospital, McKinney, Tex., and The University of Texas Southwestern Medical School, Dallas, Tex.

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*Present address: 1501 W. Tenth, Amarillo, Tex.

of whole blood was infused slowly. His blood pressure remained 70/40 mm. Hg until norepinephrine was given slowly intravenously. It was at this point that Cheyne-Stokes respiration was noted for the first time, and it persisted for the remainder of his course. His blood pressure rose to 140/110 mm. Hg and for the rest of hospitalization fluctuated between 70/50 and 160/110 mm. Hg. The patient became quite alert and asymptomatic, and experienced no further neurologic manifestations until the fifth hospital day. At that time he began to have frequent episodes of tonic convulsive seizures during which almost continuous electrocardiograms were taken. He was then given 10 per cent dextrose in distilled water with 40 meq. of potassium and 0.5 Gm. amino-

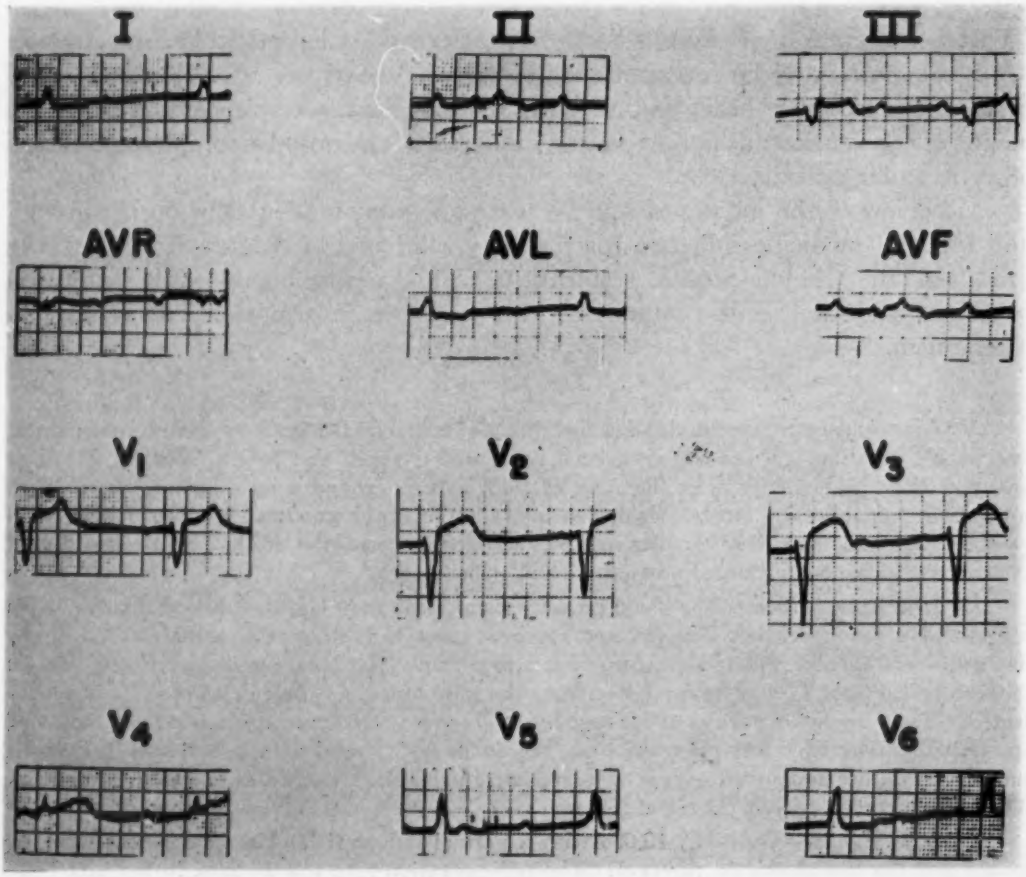

Fig. 1.—Electrocardiogram on admission showing complete heart block with an idioventricular rhythm. Atrial rate is 107 per minute and ventricular rate is 43 per minute. RS-T segment changes in V_2 and V_3 are compatible with acute anteroseptal myocardial ischemia.

phylline. About two hours before the patient expired it was noted that he had long periods of ventricular standstill and, furthermore, that the asystole was coinciding in onset and duration with the hyperpneic phase of the Cheyne-Stokes respiration. The hyperpnea actually began two cardiac cycles prior to the onset of ventricular standstill. Within two to three seconds after the beginning of each apneic period QRS complexes were again seen on the electrocardiogram (Fig. 2). During the times of ventricular standstill and hyperpneic respiration the patient had mild tonic convulsions of all extremities. This pattern continued for one to two hours when he had complete cardiac standstill which responded only briefly to needle agitation of the myocardium (Fig. 3).

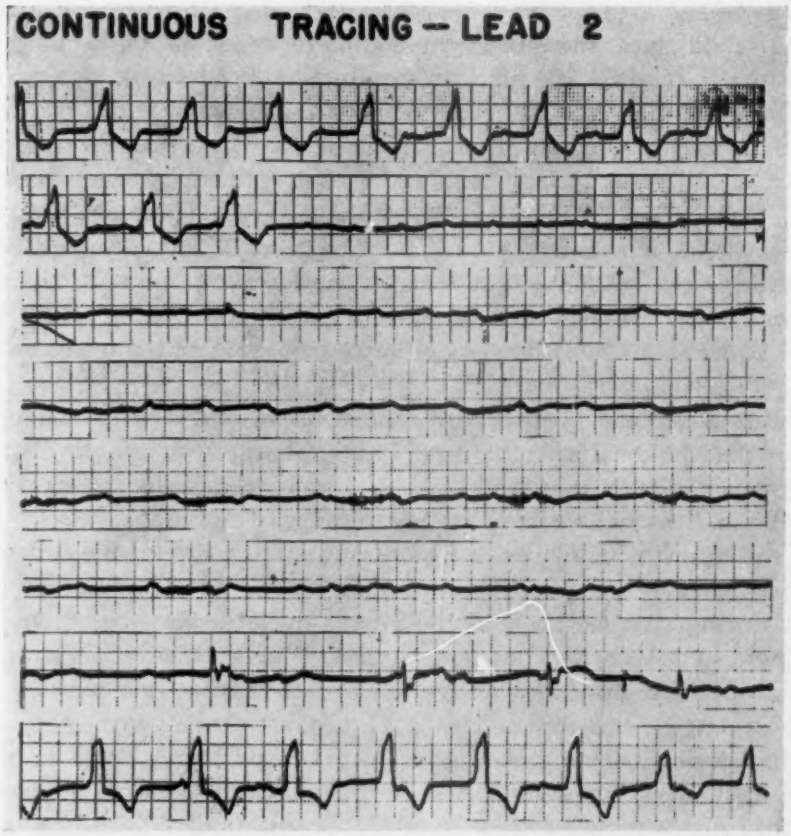

Fig. 2.—Lead II taken several hours before death showing a period of ventricular asystole associated with the hyperpneic phase of Cheyne-Stokes breathing. The artifacts due to respiratory movement are readily seen.

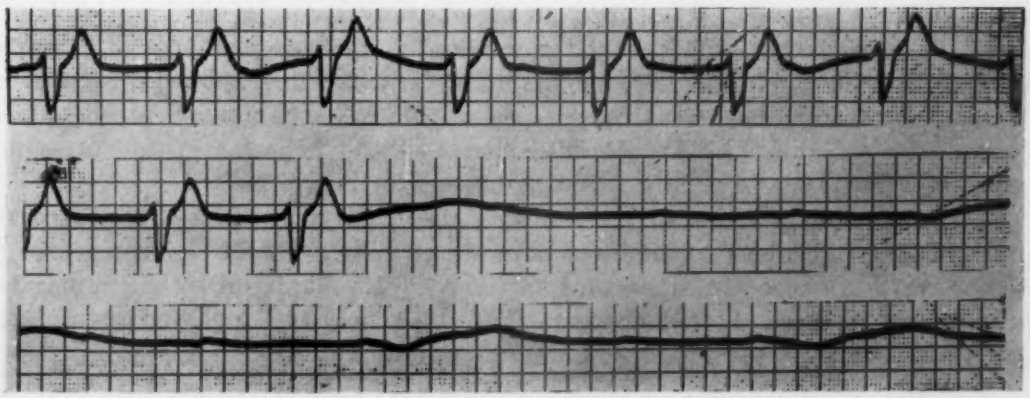

Fig. 3.—Lead III taken after complete standstill had responded only briefly to needle agitation of the myocardium.

DISCUSSION

Adams-Stokes attacks may be associated with Cheyne-Stokes respiration in two quite different manners. In complete heart block cardiac standstill as the primary disturbance may precipitate hyperpnea followed by apnea. Rarely, Adams-Stokes attacks may occur so frequently that the respiration approaches typical Cheyne-Stokes periodicity. This sequence, mentioned in texts by Goldberger[2] and Friedberg,[3] is exemplified by four cases reported by Averbuck,[4] Dlugacz,[5] Hill and MacKinnon,[6] and Thomas.[7] On the other hand, in patients with an established pattern of Cheyne-Stokes respiration, Adams-Stokes attacks may supervene during each period of hypernea. In this sequence, the cardiac dysfunction is caused by the periodic breathing. The cases of Baumler,[1] Anthony, Cohn, and Steele,[8] and the present case are instances of this phenomenon.

In the present case, Adams-Stokes seizures were due to failure of the idioventricular pacemaker during the hyperpneic phase. Some light on the mechanism of this ventricular standstill may be shed by reviewing the cardiac slowing during Cheyne-Stokes breathing noted frequently for many years. The literature on the effect of Cheyne-Stokes breathing on cardiac rate and mechanism was succinctly reviewed by Matthews and Wood,[9] in 1940. Some slowing of the heart during part of the Cheyne-Stokes cycle is very common. Interestingly enough, in central nervous system disease with periodic breathing, slowing usually occurs with apnea, whereas in cardiac disease the slowing is almost always associated with hyperpnea. The bradycardia with cardiac disease may be due to sinus slowing, A-V nodal rhythm, partial A-V block, or complete heart block. There are several cases[9-11] in which A-V block appeared, or increased, during hyperpnea and receded, or disappeared, during apnea. In these cases, abolishing the block by atropine, and exaggerating it by carotid sinus pressure, seems to establish an action of the vagus in provoking the block. Since the hyperpneic period of Cheyne-Stokes breathing is one of arterial hypoxia,[12] and since severe hypoxia can produce heart block in animals,[11,13] it appears likely that the vagus is reflexly stimulated to produce heart block by arterial hypoxia, presumably acting on the chemoreceptors of the carotid sinus.

The present case differs from the previously reported instances of Adams-Stokes attacks produced by Cheyne-Stokes respiration in that the cardiac mechanism throughout was complete heart block. The failure of the idioventricular pacemaker to fire during hypernea could be due to the depressant effect of arterial hypoxia on a severely diseased myocardium.

The seeming paradox of arterial hypoxia and hypercapnea during hyperpnea may be explained by the inordinately long delay,[14,15] mostly intracardiac,[16] in the transit of blood from alveoli to arteries which characterize the circulation of severely diseased dilated hearts. This delay may well be fundamental to the genesis of Cheyne-Stokes breathing associated with cardiac disease.[17]

SUMMARY

1. A case is presented of Cheyne-Stokes respiration with directly related Adams-Stokes attacks and in which the basic cardiac rhythm is complete heart block.

2. Previous studies of Cheyne-Stokes associated with Adams-Stokes are reviewed and the two quite different manners by which this association may come about are stressed.

3. The importance of arterial hypoxia superimposed on complete heart block and as a probable cause of periodic breathing is suggested.

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COMPLETE HEART BLOCK WITH PERFORATED INTERVENTRICULAR SEPTUM FOLLOWING CONTUSION OF THE CHEST

CLAUDE PAULIN, M.D., AND IRA L. RUBIN, M.D.

NEW YORK, N. Y.

TRAUMA to the heart is not uncommon; it may be due to direct injury from a penetrating wound or a nonpenetrating injury due to blunt force. The latter may cause injury to or rupture of the muscle of any chamber of the heart.[1] The exact mechanism of rupture due to nonpenetrating injury has not been clearly elucidated.

Isolated rupture of the interventricular septum due to blunt injury has been a rare phenomenon. In 1952, Pollack and associates[2] were able to compile only thirteen reported cases. We have been able to find one other case reported since.[3] Post-mortem examination had been the only way of comfirming the diagnosis. Recently cardiac catheterization has been used to establish the diagnosis ante mortem.[3,4] On examination these patients usually have a harsh systolic murmur heard in the fourth and fifth intercostal spaces to the left of the sternum, similar to congenital interventricular septal defect. If the rent is over 2 cm. in diameter, a diastolic murmur may also be heard.[4] Large rents may be associated with no murmur. No murmur may be heard if the patient is in shock. Clinically, patients with a traumatic rupture of the interventricular septum resemble those following myocardial infarction. There may be shock, cyanosis, dyspnea, and orthopnea and left-sided and later right-sided failure. These patients may live only a few minutes to hours or survive without difficulty up to eleven years.[1] Cases of presumed ruptured interventricular septum following trauma have been reported with persistance of the bruit and murmur and apparent good health for many years.[8-10]

Complete heart block has been produced in dogs experimentally following nonpenetrating injury.[5] In experimental animals, the heart block is usually transient. In humans, heart block has followed nonpenetrating chest injury; it is frequently transient but may persist for many years. Coffen,[6] in 1941, was able to find only six cases of heart block following nonpenetrating injury proved by graphic record. In 1943, Arenberg reported another case. Other cases of traumatic heart block have been reported without graphic records; these have not been included in the report.

The combination of heart block with proved ruptured interventricular septum has not been reported. The following is a case report of an apparently healthy young man who suffered complete heart block and a ruptured interventricular septum following a nonpenetrating chest injury.

From Cardiovascular Service, Morissania City Hospital, Dr. Julius Burstein, Director.
Received for publication March 20, 1956.

CASE REPORT

The patient was a 19-year-old Puerto Rican boy who was in good health until 5 P.M. on March 26, 1955, when he was in an accident. The car he was driving struck a tree. The patient became unconscious. Past history obtained for the patient's mother revealed no history of cardiac disease or murmur. He had had tetanus at age fifteen. On admission to the hospital a short time later, he was in shock, restless, and complaining of chest pain. Physical examination revealed the blood pressure to be 90/70 mm. Hg. There were numerous contusions of the scalp and numerous lacerations about the mouth, gums, face, and legs. There was a contusion of the anterior chest wall. The heart sounds were distant but no murmurs were heard. There were no signs of congestive heart failure or venous distension. He was treated with intravenous noradrenalin, oxygen, and morphine. Five hundred cubic centimeters of blood was administered.

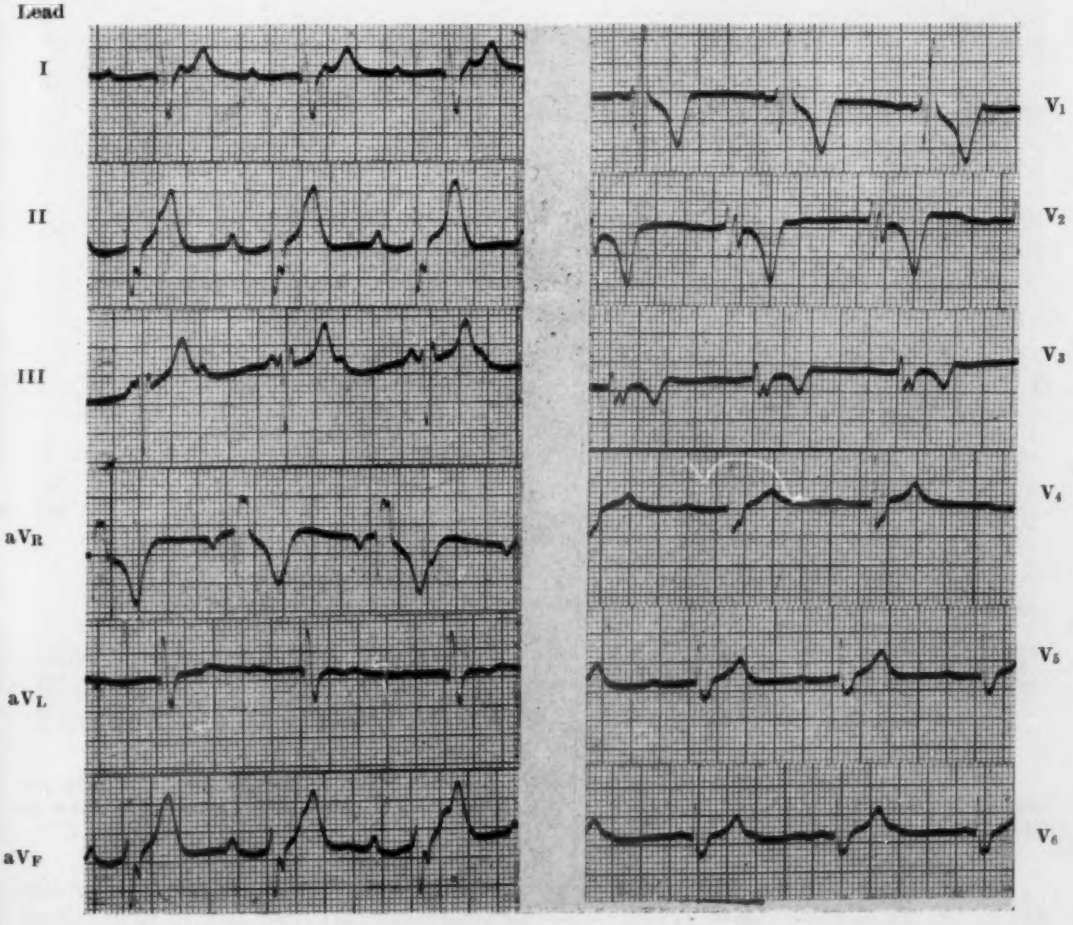

Fig. 1.—Electrocardiogram taken three hours after admission. There is complete dissociation with a ventricular rate of 60 per minute and an auricular rate of 125 per minute. Note QRS measures 0.12 sec

Three hours after admission, the patient complained of severe substernal oppression and difficulty in breathing. The blood pressure was 90/40 mm. Hg. A roentgenogram of the chest revealed no evidence of pneumothorax or pulmonic infiltration. An electrocardiogram (Fig. 1) showed complete heart block with a ventricular rate of 60 per minute and an auricular rate of 125 per minute. The QRS measured 0.12 second with a pattern resembling right bundle branch block. There were deeply inverted T waves in V_1, V_2, and V_3.

Five hours after admission, the patient was still in shock. An electrocardiogram (Fig. 2) revealed a ventricular rate between 29 and 30 per minute. The QRS complex now measured

0.16 second and small Q waves were present between V_1 and V_2. Despite the absence of venous distension, cardiac tamponade was considered. To rule out this possibility, a pericardial tap was performed. Only a few cubic centimeters of blood was obtained; a transient ventricular tachycardia was produced. Though an infusion of noradrenalin was maintained, the patient remained in shock and gradually lapsed into coma.

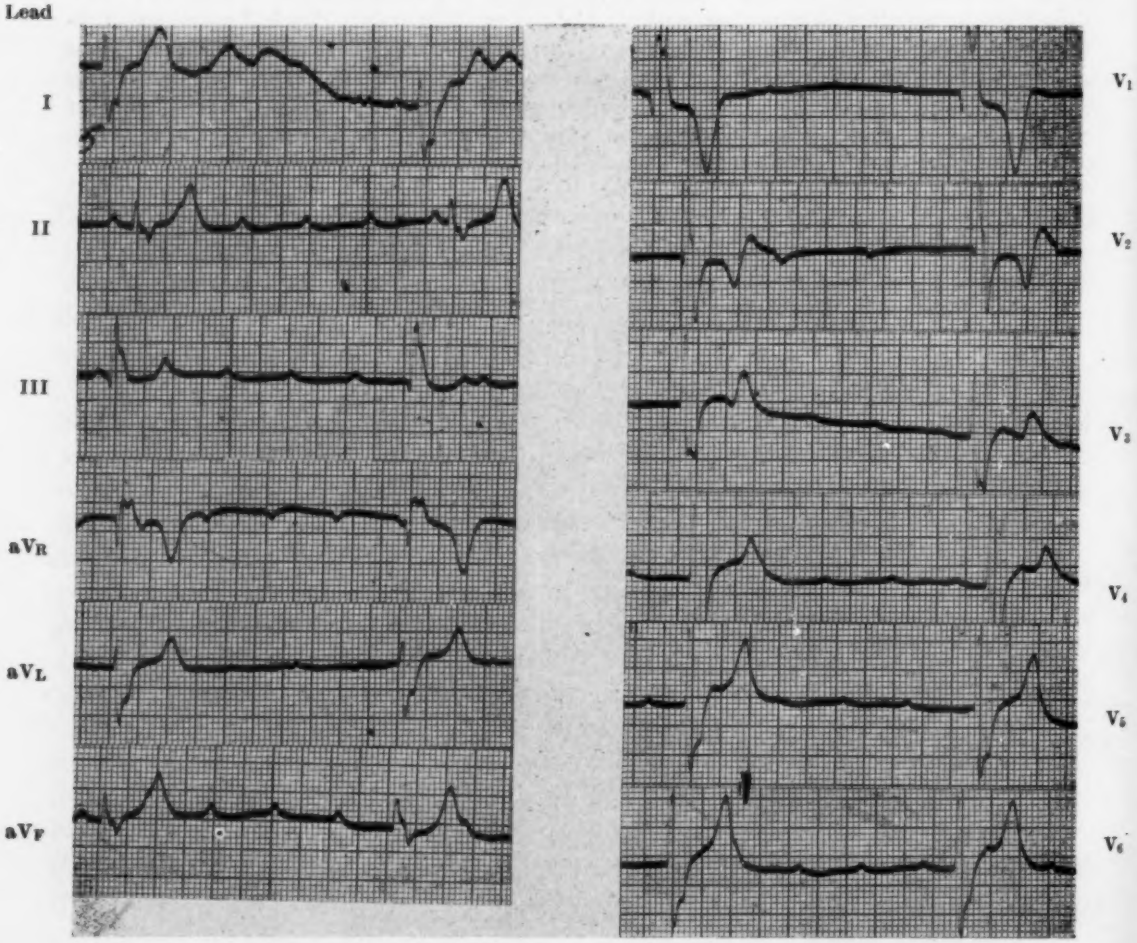

Fig. 2.—Electrocardiogram taken five hours after admission. The ventricular rate is 29 to 30 per minute; the auricular rate is 136 per minute. Note QRS measures 16 sec. and presence of Q waves in V_1 and V_2.

Eight and one-half hours after admission, his ventricular rate was 25 and his auricular rate 150 to 160 per minute. There was an occasional ventricular beat from another focus. Nine hours after admission, another pericardial tap was attempted without finding blood or fluid; again a short run of ventricular tachycardia was induced. The ventricular rate returned to about 29 per minute with slight variation in the duration, size, and shape of the QRS complexes. The patient remained in coma and shock and died twenty-three hours after admission. At no time was a cardiac murmur noted; there was no venous distension or signs of failure.

On autopsy, performed by the Medical Examiners Office of the City of New York, multiple contusions of both sides of the chest wall were noted. The heart showed an opening between the right and left ventricles due to a fresh laceration three-quarters of an inch in diameter. There was a large tear in the interventricular septum. No blood was noted in the pericardial cavity. In addition, fracture and dislocation of the third and fourth cervical vertebrae with compression of the cord was observed. Microscopic examination was not performed.

DISCUSSION

In the case reported above, the patient was an apparently healthy young man who suffered a severe contusion of the chest from a steering-wheel injury. There was no fracture of the rib cage noted either clinically, roentgenographically, or on post-mortem examinations. No murmur was detected at any time. The absence of a murmur may have been related to the low blood pressure and shock-like state of the patient. The slow ventricular rate was noted on admission to the hospital. Cardiac trauma was diagnosed clinically because of the finding of heart block. Despite the absence of venous distension and heart failure, pericardial tamponade was suspected and two unsuccessful pericardial taps performed. The exact cause of death is not certain. Severe neurologic injury was also present. The progressive slowing of the cardiac rate, the shock, and the appearance of Q waves in V_1 and V_2 (Fig. 2) reflected serious myocardial injury. It is not certain that the patient would have survived if neurologic damage had not simultaneously occurred.

SUMMARY

The case history of an apparently healthy young man who died following a nonpenetrating trauma to the chest from a steering-wheel accident is reported. Clinically, complete heart block was noted; pathologically, a ruptured interventricular septum was found.

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A PRECORDIAL SYSTOLIC MURMUR OF EXTRACARDIAC ORIGIN DURING PREGANCY

ROBERT P. GRANT, M.D.

BETHESDA, MD.

PRECORDIAL systolic murmurs have been frequently noted to develop in the course of pregnancy. Their origins have been thought variously to be due to increased blood velocity, tortuosity of the internal mammary artery, or kinking of the pulmonary artery due to elevation of the diaphragm. Usually these murmurs are faint and rarely do they suggest that organic heart disease is present. However, two patients have been observed in whom the murmur was of such loudness that organic heart disease was suspected. In both cases it was possible to prove that the murmurs were benign and of extracardiac origin.

The first patient was a 22-year-old primagravida who was seen in her eighth month of pregnancy because of a loud systolic murmur. On examination the murmur was of Grade 4 intensity, localized to a small region in the third intercostal space to the left of the sternum. It was high pitched and extended into early diastole. Although the murmur had not been heard during a previous hospitalization two years earlier, its loudness and location suggested that it might be due to a patent ductus arteriosus. The pulse pressure, chest roentgenogram, and remainder of the cardiac examination were entirely normal. On more careful examination it was found that at one point in the region of the chest where the murmur was heard, gentle but firm pressure on the stethoscope bell could cause the murmur to vanish while the heart sounds remained audible. The pregnancy was completed uneventfully and the murmur vanished shortly after lactation began.

The second patient was a 32-year-old primigravida graduate nurse, who was seen in her third month of pregnancy because of a loud murmur. She had had an episode of chronic fever of unknown origin several years previously. During the years since that illness she had had mild joint pains with occasional swelling of interphalangeal joints which were thought to be due to chronic rheumatoid arthritis. One afternoon during her third month of pregnancy, after a strenuous day of protracted standing and walking, she noted a cluster of tiny petechial hemorrhages on her inner left thigh and immediately consulted her physician. At this time a Grade 3 systolic murmur was heard over the base of the heart for the first time. In view of the previous history of obscure fever, rheumatoid arthritis, petechiae, and "changing murmurs," a diagnosis of subacute bacterial endocarditis was entertained and she was immediately hospitalized. Physical

From the Clinic of General Medicine and Experimental Therapeutics, National Heart Institute, Bethesda, Md.

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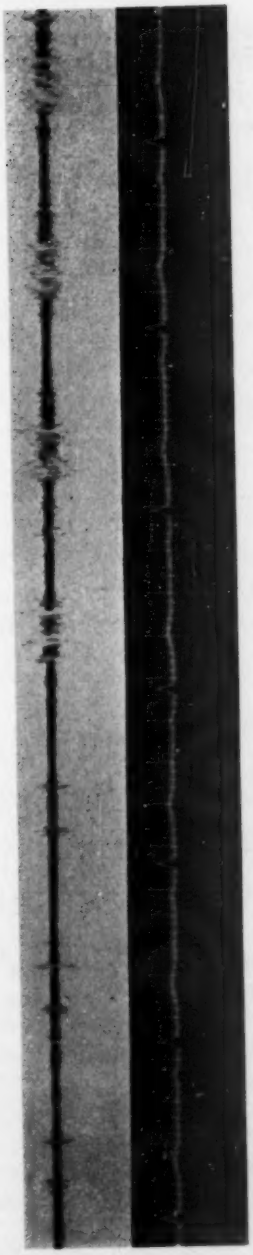

Fig. 1.—Simultaneous phonocardiogram and electrocardiogram. On reducing the pressure on the recording microphone a loud systolic murmur appears.

examination at this time disclosed the pregnancy, the petechiae, and the murmur, but was otherwise normal. Laboratory studies including numerous blood cultures were negative. On careful study of the murmur, it was noted that it was harsh, high-pitched, late systolic, and localized, an area of only 4 to 5 cm. in diameter in the third intercostal space to the left of the sternum. On full inspiration the murmur did not alter in intensity while the other cardiac sounds became fainter. As in the previous case, it was found that at one point on the medial region of the area where the murmur was heard, firm pressure by the stethoscope bell would invariably cause the murmur to vanish for the duration of the pressure while the heart sound remained audible. In Fig. 1 is shown a phonocardiographic tracing illustrating the return of the systolic murmur on release of pressure on the stethoscope bell. The remainder of the cardiac examination was negative. Her breasts were considerably enlarged by the pregnant state. No arterial pulsation could be felt in the region where pressure by the stethoscope bell caused the murmur to disappear. The pregnancy was completed uneventfully and the murmur disappeared shortly after lactation began.

SUMMARY

Two cases are presented where loud precordial systolic murmurs were heard over the base of the heart during pregnancy. In both cases pressure by the stethoscope bell at a point in the region where the murmur was heard caused it to vanish. It is concluded that the murmur was due to an engorged tortuous mammary vessel.

Announcements

A steering committee of some fifty scientists, representing various aspects of biophysical research in this country, has organized a NATIONAL BIOPHYSICS CONFERENCE to take place in Columbus, Ohio, from March 4 to 6, 1957. The conference will encompass studies which employ the approach of physics in biological measurement and theory, at levels of organization from molecules and cells to complex systems and psychophysics.

The program is expected to include twelve invited papers related to different biophysical fields and a large number of contributed papers. Scientists with biophysical interests may write for further details and information on presenting contributed papers to: Dr. Herman P. Schwan, Chairman, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

A SYMPOSIUM ON "THE PRESENT STATUS OF HEART SOUND PRODUCTION AND RECORDING" will be held at the University of Buffalo, Buffalo, N. Y., on Feb. 14, 1957. The meeting will be co-sponsored by the University of Buffalo and the Buffalo-Niagara Chapter of the Professional Group on Medical Electronics. It is planned to cover the physical characteristics of the heart sounds, problems of instrumentation, and newer techniques of heart sound analysis. Those interested in attending or contributing to the program are invited to communicate with the Program Chairman, Dr. Robert M. Kohn, at the Chronic Disease Research Institute of the University of Buffalo, 2183 Main Street, Buffalo 14, N. Y.

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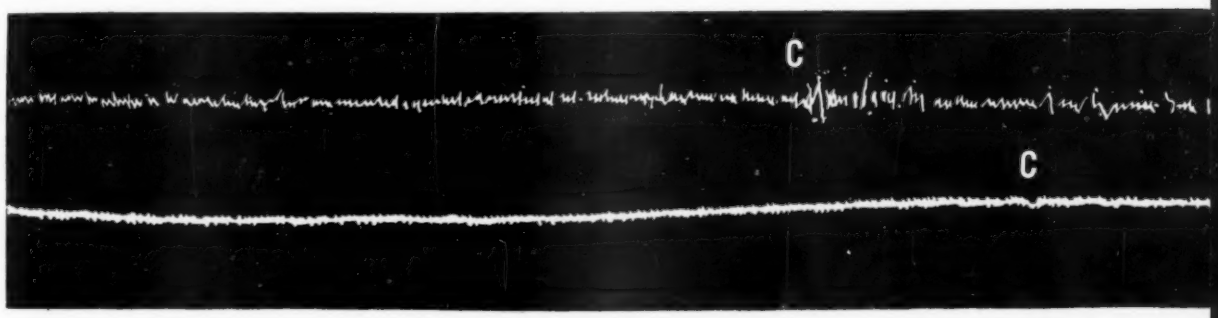

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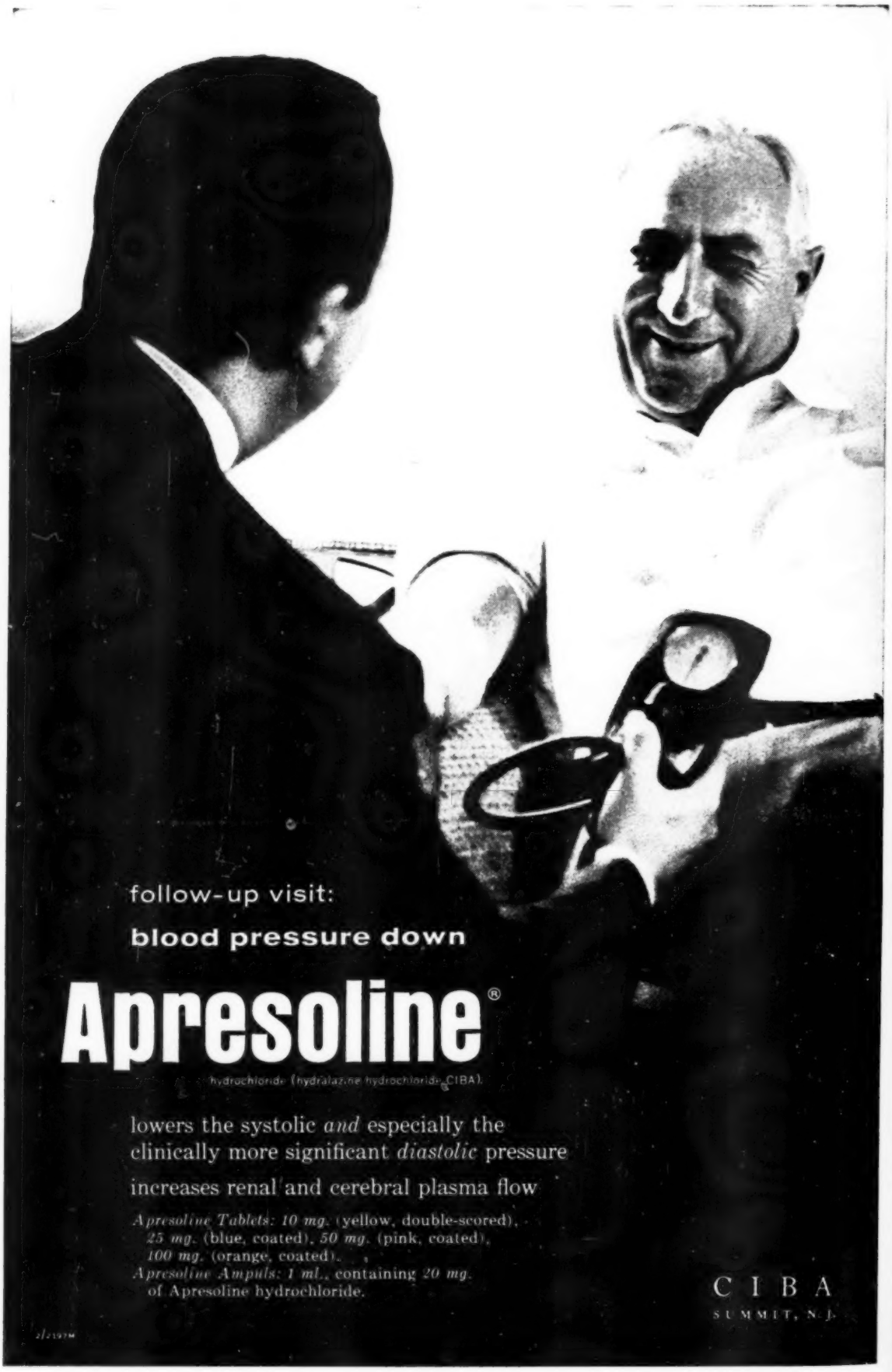
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lowers the systolic *and* especially the clinically more significant *diastolic* pressure
increases renal and cerebral plasma flow
Apresoline Tablets: 10 mg. (yellow, double-scored), *25 mg.* (blue, coated), *50 mg.* (pink, coated), *100 mg.* (orange, coated).
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PRACTICAL THERAPEUTICS

in **ANGINA PECTORIS**

PROTECT the PATIENT
A-L-L D-A-Y L-O-N-G
with

COROVAS

TYMCAPS

Pentaerythritol tetranitrate 30 mg.
Secobarbituric acid 50 mg.
in a capsule of timed-disintegration pellets.

- P-R-O-L-O-N-G-E-D PROPHYLAXIS . . .
- 24-HOUR FREEDOM FROM CORONARY VASOCONSTRICTION, MORE UNIFORM BLOOD LEVELS, FEWER SIDE EFFECTS, AND NO REPORT OF ACQUIRED TOLERANCE . . .

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2 COROVAS *TYMCAPS*, one every 12 hours, will prolong effective coronary vasodilation and free the patient from pain, fear and the risk of cardiac failure for a full twenty-four hours . . .

COROVAS *TYMCAPS are available in bottles of 60, 120, 500 and 1000. For further data and a generous trial supply of* **COROVAS** *TYMCAPS, write to Medical Director.*

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DIGOXIN

formerly known as Digoxin 'B. W. & Co.'®

The new name has been adopted
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the distinction between
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Now simply write: 'Lanoxin' Tablets 0.25 mg. or 0.5 mg.
'Lanoxin' Elixir Pediatric, or
'Lanoxin' Injection

to provide the unchanging safety and predictability afforded by the uniform potency, uniform absorption, brief latent period and optimum rate of elimination of this crystalline glycoside.

Tablets: *0.25 mg. (white) and 0.5 mg. (green)*
Elixir Pediatric: *0.05 mg. in each cc.*
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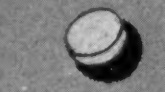
to prevent anginal attacks—

which will you prescribe next time?



4 hour protection

1 PETN Tablet (pentaerythritol tetranitrate)

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1 PENTRITOL Tempule (pentaerythritol tetranitrate)

Now, for the first time, you can protect anginal patients with *Pentritol's* uninterrupted prophylaxis. One Pentritol Tempule on arising and a second twelve hours later maintains coronary vasodilation 24 hours a day. This continuous protection was virtually impossible with 4-hour tablets of PETN. Pentritol prevents attacks which were precipitated by medication-gap. Your patients' response to uninterrupted prophylaxis will demonstrate the advantages of Pentritol.

Samples and literature on request.

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*controlled disintegration capsules of 30 mg. pentaerythritol tetranitrate (PETN). Also available, Pentritol-B Tempules with 50 mg butabarbital added.

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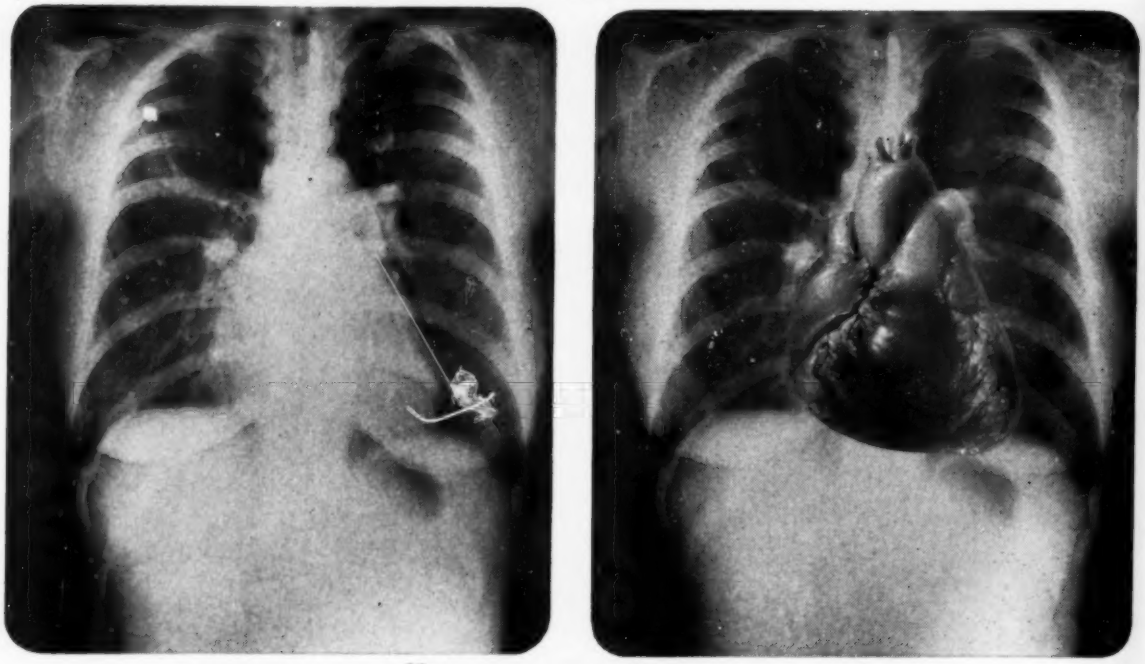
VISUAL HEART CLINIC—NUMBER ONE OF A SERIES



RHEUMATIC HEART DISEASE • MITRAL STENOSIS AND INSUFFICIENCY

ROENTGEN CONFIGURATION—Postero-anterior examination—moderate heart enlargement—right ventricular enlargement—prominence of pulmonary artery segment.

Taken from White Laboratories' Technical Exhibit, American Medical Association 105th Annual Meeting, Chicago, June 11-15, 1956.

Every year since 1950 when Batterman, et al., published the results of their study of 230 cardiac patients, clinical evidence has repeatedly confirmed the therapeutic advantages of GITALIGIN.

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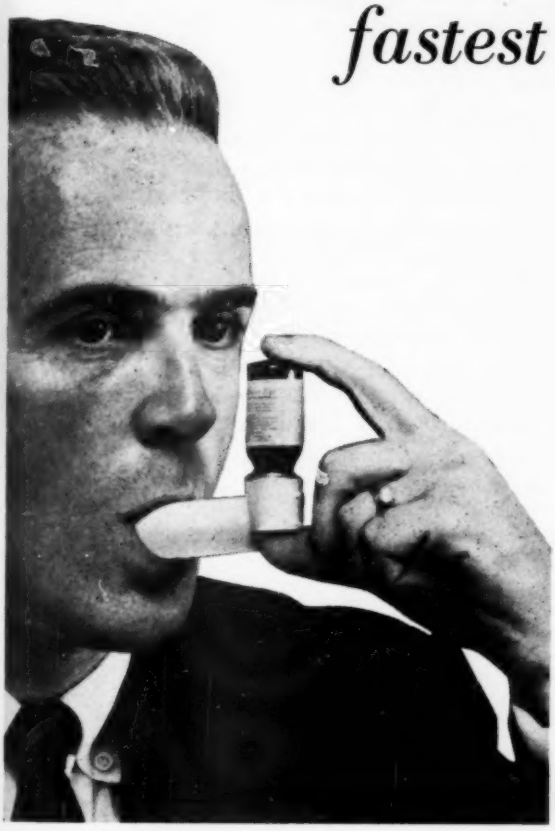
*EHRLICH, J.C.: ARIZONA MED. 12:239 (JUNE) 1955. BIBLIOGRAPHY FURNISHED ON REQUEST

In Angina Pectoris

Medihaler-Nitro



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MEDIHALER...The New Measured-Dose Principle of Nebulization

and for definitive therapy... fewer and fewer attacks of less and less intensity

Long-acting tablets containing pentaerythritol tetranitrate (PETN) 10 mg. and Rauwiloid® (alseroxylon) 1 mg. reduce the incidence and intensity of attacks and lead to objective improvement demonstrable by ECG. Dosage: one or two tablets q.i.d., before meals and on retiring

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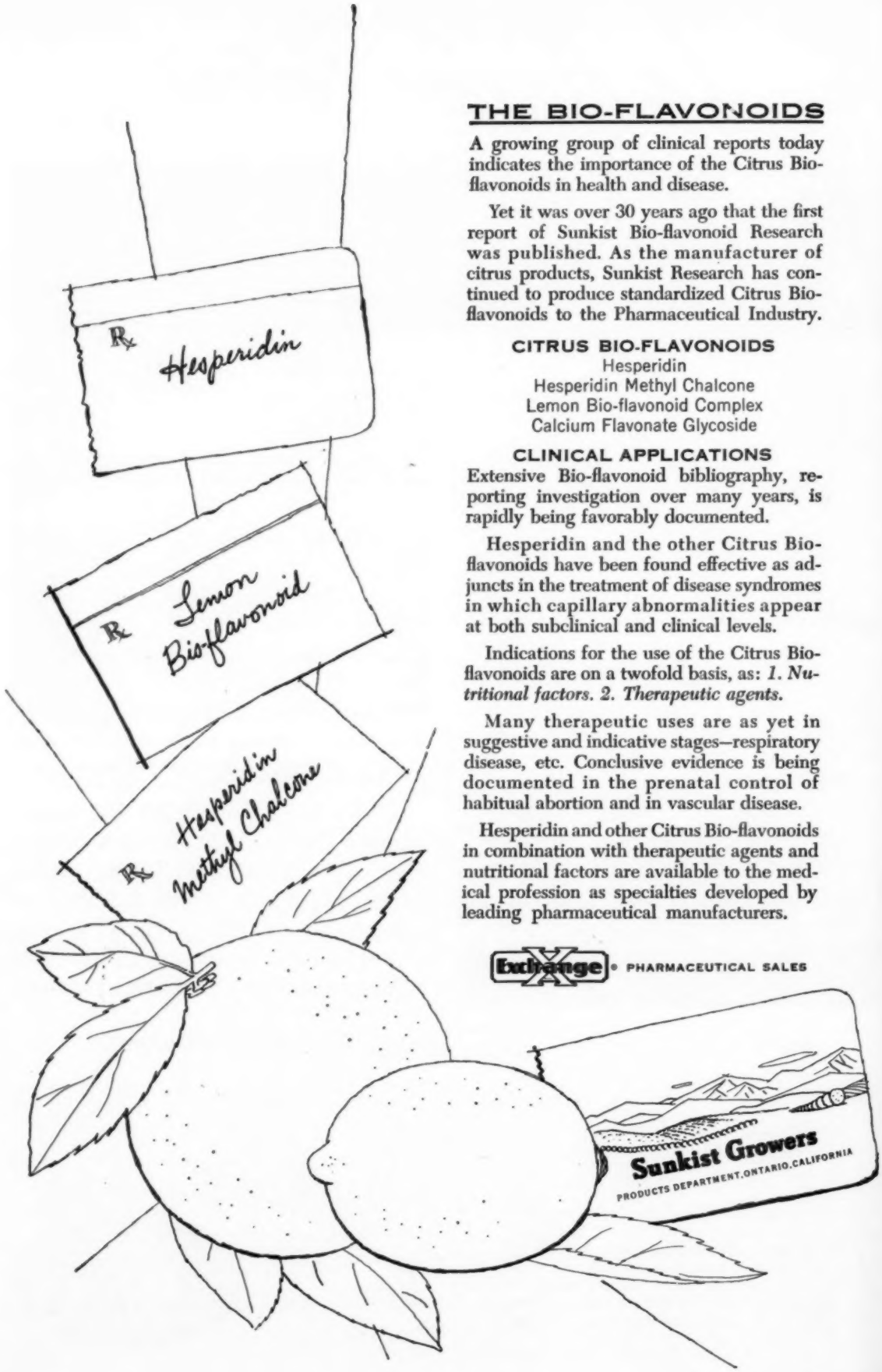
Riker
LOS ANGELES



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It is now possible to maintain a balance between fluid/salt intake and output with only 1 or 2 CUMERTILIN Tablets daily.[1-5] Dann and associates[1] report that CUMERTILIN Tablets have been taken safely *without interruption* for periods ranging up to three years. Thus, following an initial mercurial diuretic injection, CUMERTILIN Tablets conveniently maintained cardiac compensation between office visits. CUMERTILIN is indicated in all types of salt-retention edema, as in congestive heart failure.

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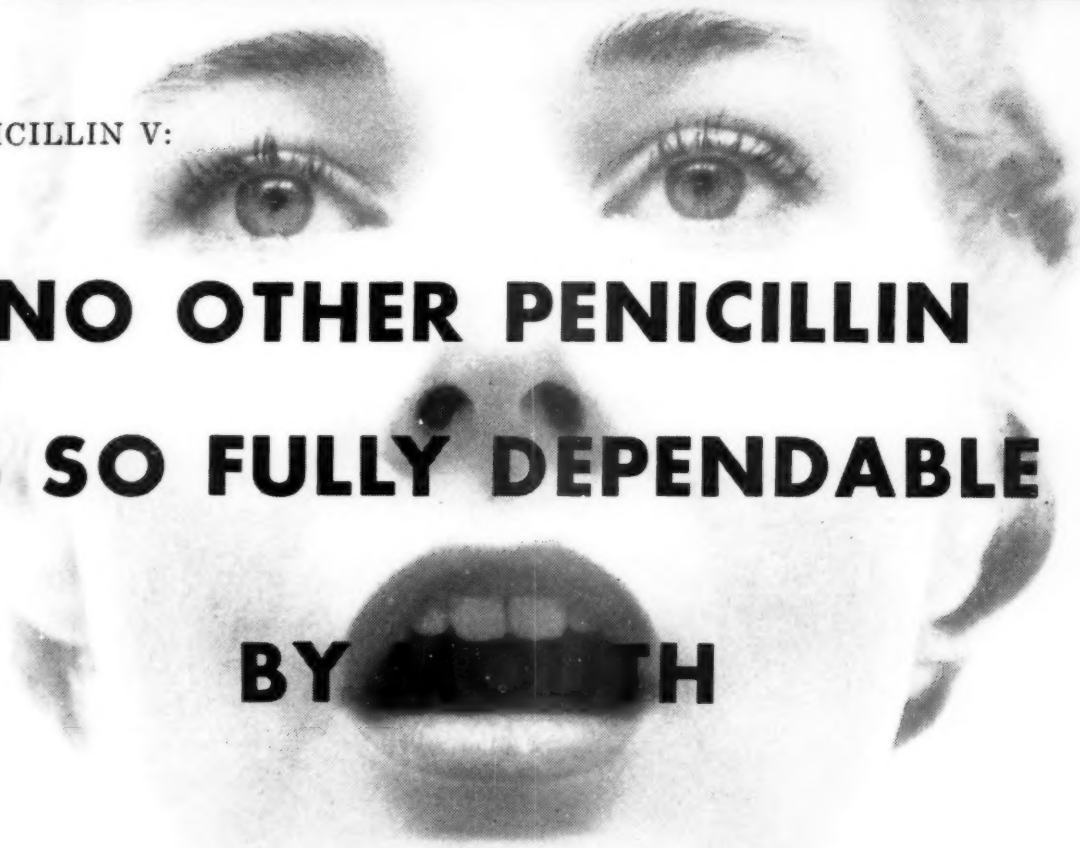
1. Dann, S.; Gutner, L. B.; Berger, A. R., and Kupperman, H. S.: *Report of a three-year clinical experience with mercumatilin,* New York J. Med. 56:1448, 1956. 2. Batterman, R. C.: *The comparative diuretic effectiveness of mercumatilin and meralluride with and without concomitant administration of ammonium chloride,* Am. Heart J. 48:780, 1954. 3. Brocato, S.: *The control of cardiac edema,* J.M.A. Georgia 43:942, 1954. 4. Pollock, B. E., and Pruitt, F. W.: *Oral therapy with mercumatilin (Cumertilin), a new mercurial diuretic,* Am. J. M. Sc. 226:172, 1953. 5. Dimitroff, S. P.: Lewis, R. C.; Thorner, M. C., and Field, J. B.: *Oral mercurial diuretics: Mercumatilin in the treatment of congestive heart failure,* Am. Heart J. 49:407, 1955.

PENICILLIN V:



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". . . the great proportion of the drug administered passes through the stomach unaltered. . . ."[1]

. . . *dependably* absorbed

". . . and reaches the intestine where absorption readily takes place. . . ."[1]

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". . . for the first time we can obtain blood concentrations with oral administration that are similar to those obtained with intramuscular injection of penicillin G at comparable doses."[1]

1. Welch, H.: Antibiotic Med. *2*:11 (Jan.) 1956.

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reduce plasma cholesterol

levels

"safely"

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ORAL

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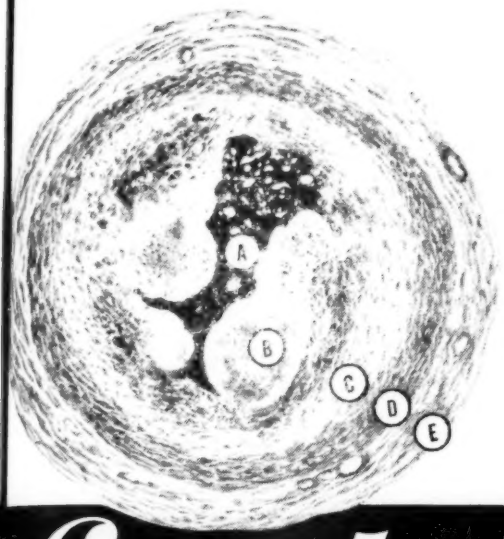
VASTRAN FORTE′ offers an important new approach to the management of atherosclerosis, by providing nicotinic acid in high concentration to reduce plasma cholesterol levels. It also provides various factors of the B-complex to spark cellular metabolism[1,4,7] and protect against latent vitamin deficiencies that may be precipitated by large dosage of a single B factor.[3,7]

Recent clinical evidence[2,6] indicates that the administration of nicotinic acid in large doses "significantly" reduces plasma cholesterol levels in patients with hypercholesterolemia and causes the pattern of blood lipids to "change toward normal."[6]

In two independent studies[2,6] embracing a total of 86 subjects, the administration of nicotinic acid brought about reduced plasma cholesterol levels in 81.4 per cent. As one report emphasized, nicotinic acid is "a safe drug" which can favorably alter the concentration of blood lipids in hypercholesterolemic patients.[6]

Among the disorders springing from long-standing hypercholesterolemia are atherosclerosis,[5] arteriosclerosis, gallstones, strawberry gallbladder and chronic degenerative lesions of the eye.[8]

WAMPOLE
85TH
YEAR



(A) Recanalized thrombus in lumen
(B) Atheromatous plaque
(C) Fibrous intima
(D) Media
(E) Adventitia

forte'

CAPSULES

ORALLY EFFECTIVE PLASMA CHOLESTEROL REDUCER

In each VASTRAN FORTE' capsule:

Nicotinic acid	375.0 mg.
Ascorbic acid	50.0 mg.
Riboflavin	2.5 mg.
Thiamine mononitrate	5.0 mg.
Cobalamine concentrate (Vitamin B_{12} activity)	1.0 mcg
Calcium pantothenate	2.5 mg.
Pyridoxine hydrochloride	0.5 mg.

Dosage: Two capsules 4 times a day.

Supply: Bottles of 100 capsules.

References: 1. Agarwal, L. P., and Datt, K.: Am. J. Ophthalmol. 37:764, 1954. 2. Altschul, R., Hoff, A., and Stephen, J. D.: Arch. Biochem. 54:558, 1955 3. Gregory, I.: J. Mental Sci. 101:85, 1955. 4. J.A.M.A.: Editorial: Relationship of Vitamins to Enzymes 111:28, 1938. 5. Keys, A.: J. Mt. Sinai Hosp., N. Y., 20:118, 1954. 6. Parsons, W. B., Jr., Achor, R. W. P., Berge, K. G., McKenzie, B. F., and Barker, N. W.: Proc. Staff. Meet. Mayo Clin. 31:377, 1956. 7. Sebrell, W. H., and Harris, R. S.: The Vitamins; Chemistry, Physiology, Pathology. Academic Press, 1954, v. 2, p. 551. 8. Stambul, J.: The Mechanisms of Disease, Froben Press, New York, 1952, pp. 241, 280, 294, 295.

WAMPOLE LABORATORIES

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CLINICAL REPORT HIGHLIGHTS

1 In 18 patients whose concentration of plasma cholesterol was consistently higher than 250 mg. per 100 cc., the administration of nicotinic acid in high dosage reduced cholesterol levels significantly in 12.[6] The pattern of blood lipids changed toward normal in the majority of the 18 patients.

The ratio of beta-lipoprotein cholesterol to alpha$_1$-lipoprotein cholesterol decreased in 15 of the 18 patients.

Side effects were mild to moderate. Treatment was withheld for a few days in 2 cases, but was successfully resumed without recurrence of side effects.

It was concluded that nicotinic acid is a safe drug which may favorably alter the concentration of blood lipids in some patients with hypercholesterolemia.

• • •

2 When nicotinic acid was administered to 11 normal persons and 57 patients with various diseases, it reduced serum cholesterol levels in 58 of the 68 subjects.[2] Hypercholesterolemic levels were more affected than normal levels.

In contrast to nicotinic acid, nicotinamide was ineffective in reducing plasma cholesterol.

ELECTRODYNE PM-65 with *Electrocardioscope**

**optional*

A PROVEN INSTRUMENT THAT:

- Detects and treats cardiac arrest automatically.
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The 3 flat E. C. G. disk electrodes held on chest by rubber strap, afford simple, fast, external hookup.

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Other important Electrodyne instruments are: The Cardiac Pacemaker, the Cardiac Defibrillator, the Cardiac Alarm, the *External* Defibrillator and combinations of these units.

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A full day's work—without Angina Pectoris

In rigorous clinical trials,[1] METAMINE SUSTAINED improved 80 (78%) of 103 patients with angina pectoris, including a group refractory to other medication.

METAMINE SUSTAINED tablets slowly release 10 mg. of METAMINE, the unique, *amino* nitrate, to provide enduring, 12-hour protection from anginal attacks.

Simplified dosage—just 1 tablet on arising, and 1 *before* the evening meal.

Greater economy for your angina pectoris patient.

Supplied: METAMINE SUSTAINED, 10 mg., in bottles of 50 sustained release tablets. Also available: METAMINE, 2 mg., and METAMINE (2 mg.) with BUTABARBITAL (¼ gr.), bottles of 50 tablets. THOS. LEEMING & CO., INC., NEW YORK 17, N.Y.

[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Med. and Clin. Therapy, 3: 322, Oct. 1956.

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triethanolamine trinitrate biphosphate, LEEMING, 10 mg.

Sustained

Fundamental advance in the battle agains

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An oral antihypertensive that gives the convenience of oral administration, the reliability of parenteral injection

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INVERSINE is both *potent* and *reliable* on *oral* administration. It has been *proved therapeutically effective* in the treatment of hypertension, and has been used by many investigators on thousands of patients.

In one of many clinical trials,* "The over-all response rate was 92%, and 24% of the patients became normotensive." Investigators have found INVERSINE to be "... the most potent ... of the three drugs in reducing the blood pressure . . ."[1] [INVERSINE and two other ganglionic blocking agents.]

Completely absorbed when it is given by mouth, INVERSINE "... has such a gradual onset and offset of action that a continuous and effective level of blockade can be readily achieved ..."[2]

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3. *Smooth, predictable response.* In a given patient, the same dose of INVERSINE elicits the same blood pressure response, time after time, *with minimal day-to-day fluctuation.*

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INVERSINE (mecamylamine) is a very potent agent which must be used with care. Side effects observed during clinical use are due to excessive pharmacologic action, and may be minimized by careful adjustment of dosage and close supervision of the patient.

References:
1. Moyer, J. H., et al.: Drug Therapy of Hypertension: Preliminary Observations on the Clinical Use of Mecamylamine (A Ganglionic Blocking Agent) in Combination with Rauwolfia for the Treatment of Hypertension, Med. Rec. & Ann. *49*:390 (Sept.) 1955.
2. Sturgis, C. C., et al.: Advances in Internal Medicine, J. Michigan M. Soc. *55*:154 (Feb.) 1956.

*In this clinical trial all patients were given, in addition to one of the ganglionic blocking agents, a constant daily amount of reserpine.

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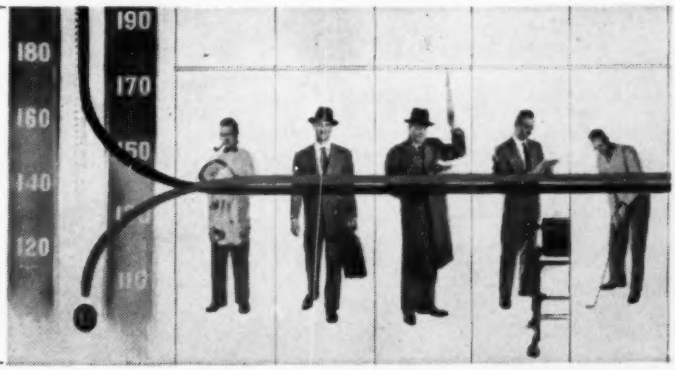
The same dose
provides
the same results
... day after day



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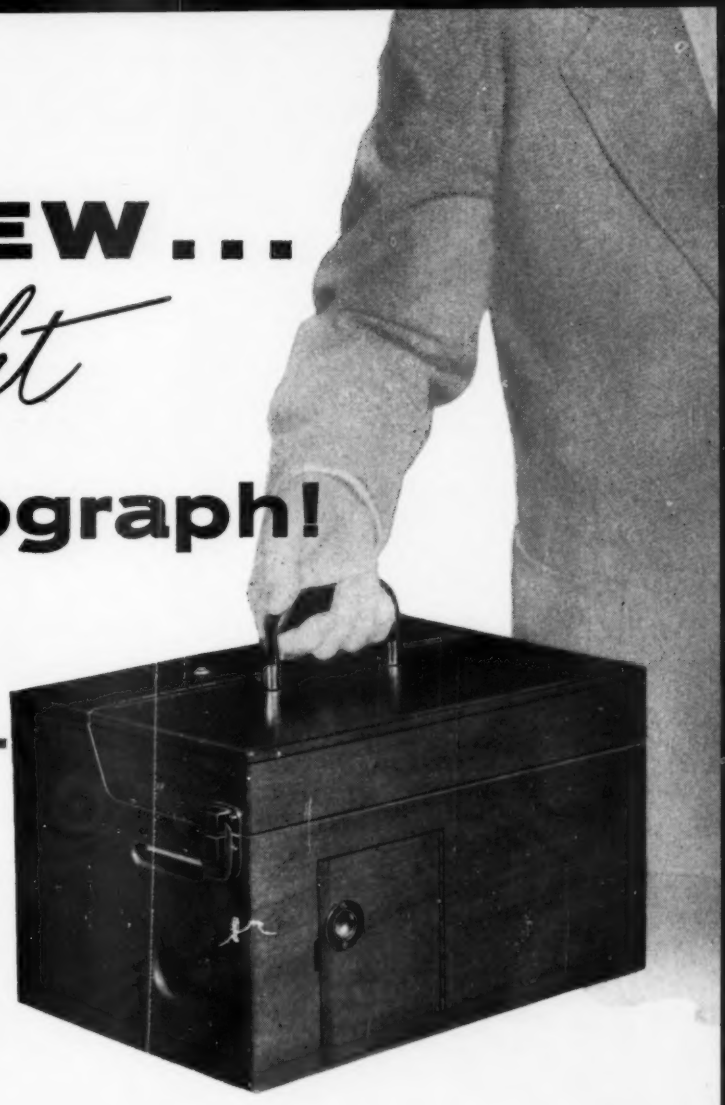

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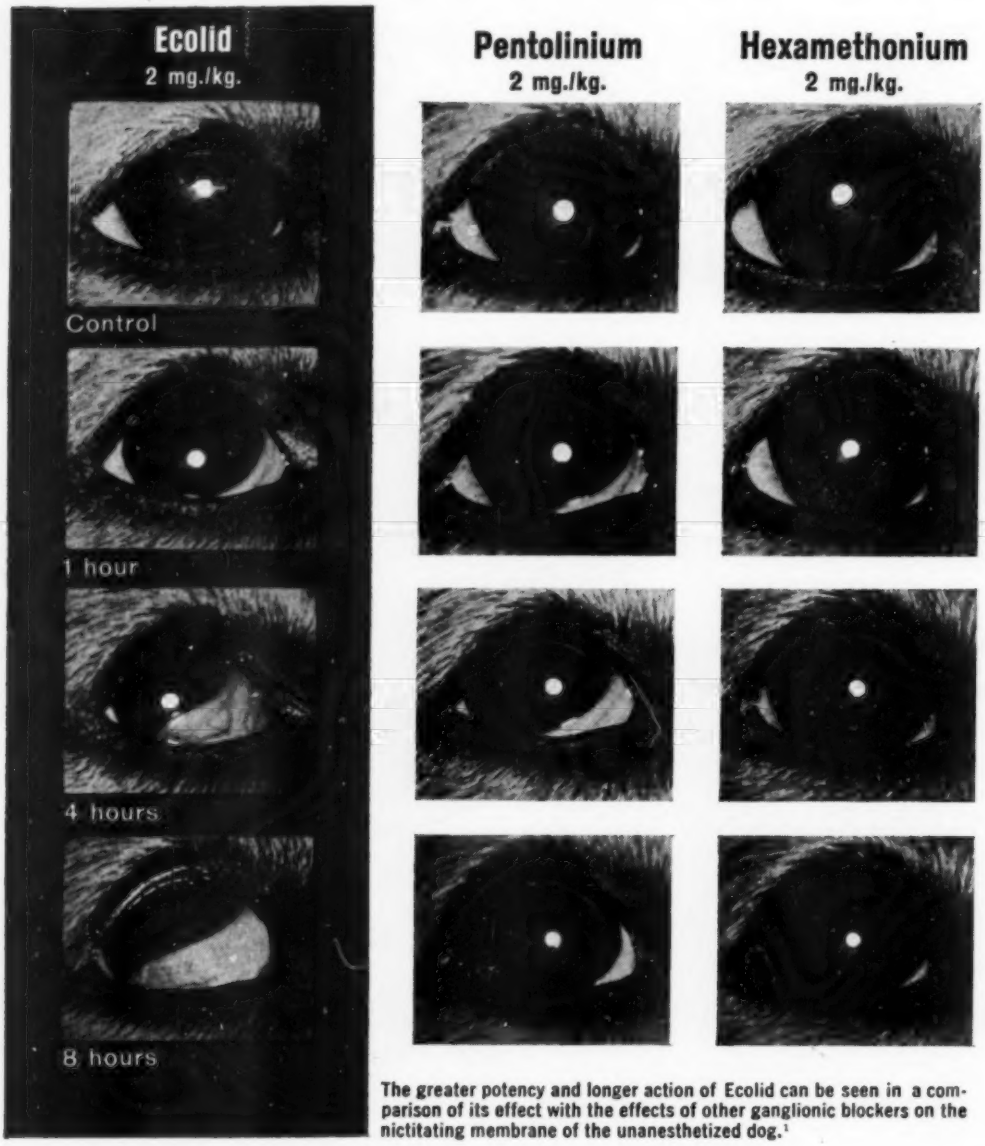

The greater potency and longer action of Ecolid can be seen in a comparison of its effect with the effects of other ganglionic blockers on the nictitating membrane of the unanesthetized dog.[1]

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1. Plummer, A. J., Trapold, J. H., Schneider, J. A., Maxwell, R. A., and Earl, A. E.: J. Pharmacol. & Exper. Therap. 115:172 (Oct.) 1955. 2. Grimson, K. S.: J.A.M.A. 158:359 (June 4) 1955. 3. Smith, J. R., and Hoobler, S. W.: Univ. Michigan M. Bull. 22:51 (Feb.) 1956. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation 11:733 (May) 1955.

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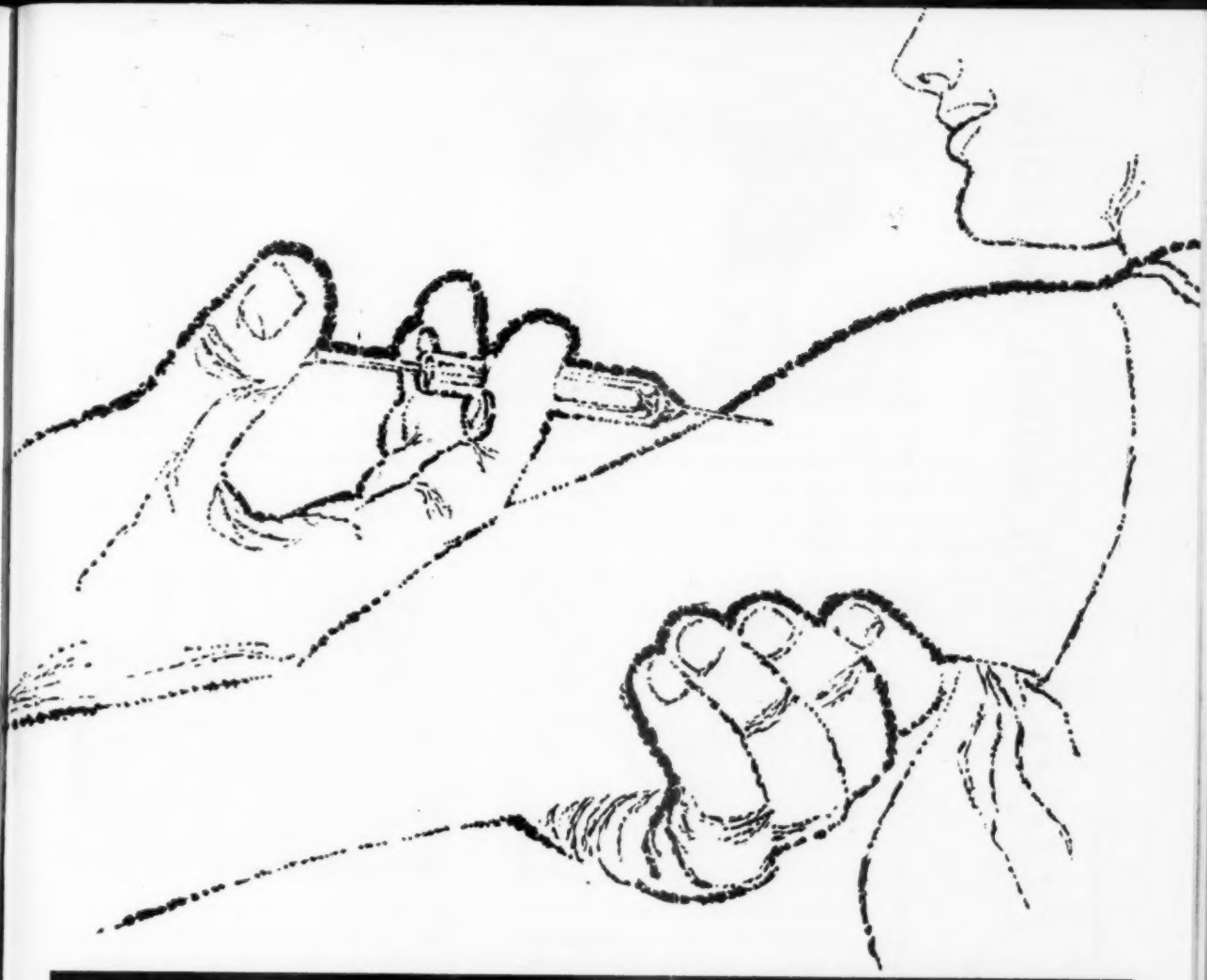

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1. New and Nonofficial Remedies. J.B. Lippincott Co., Philadelphia, 1956, p. 328. 2. Osol, A., and Farrar, G.E., Jr.: The Dispensatory of the United States of America. J.B. Lippincott Co., Philadelphia, 1956, pp. 808-809.

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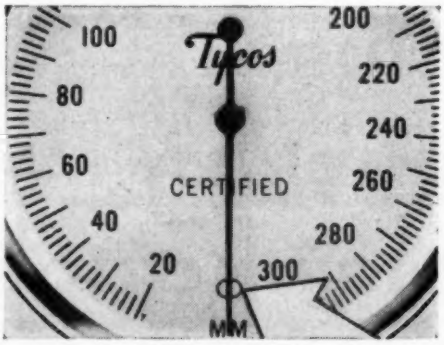

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2. What Is the Role of the More Potent Agents? ". . . the evidence . . . suggests that the technique [for the effective and safe use of such agents as ANSOLYSEN] should be more widely learned and employed. Furthermore, . . . the patients with early hypertension, especially those without renal damage, are far more easily controlled, with fewer side effects, than the patients with advanced hypertension."[1]

Freis cautions that these views are not presented as dogma; ". . . they have been developed to show the other side of an argument that seems to have many points in its favor."[1]

1. Freis, Edward D.: Guest Editorial. GP *14*:72 (July) 1956.

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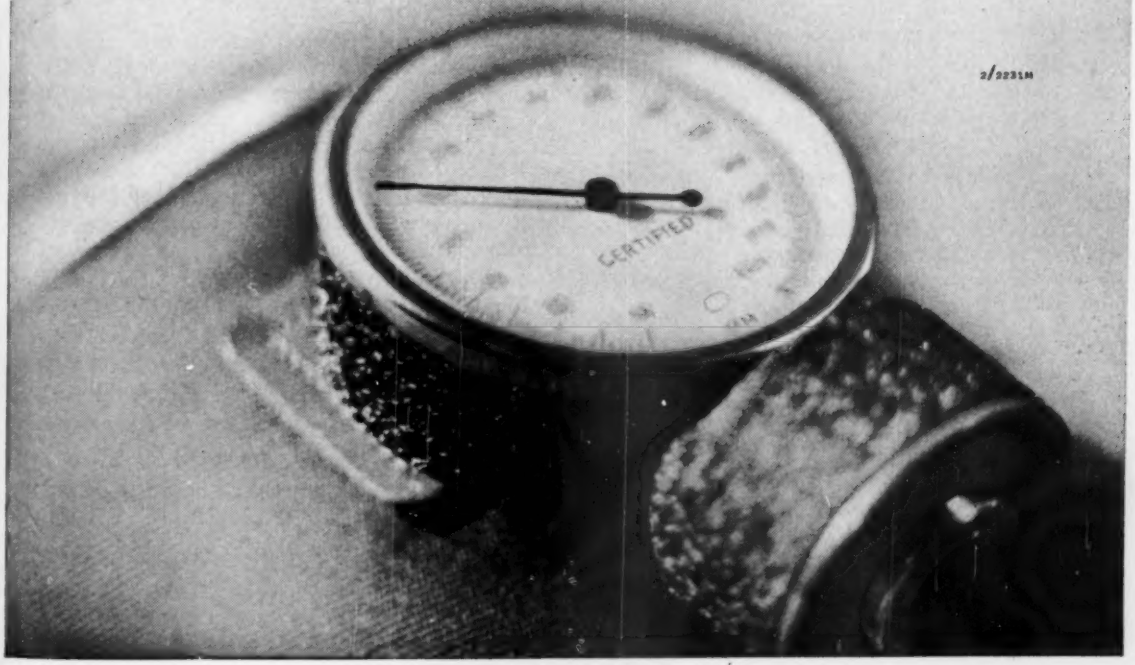

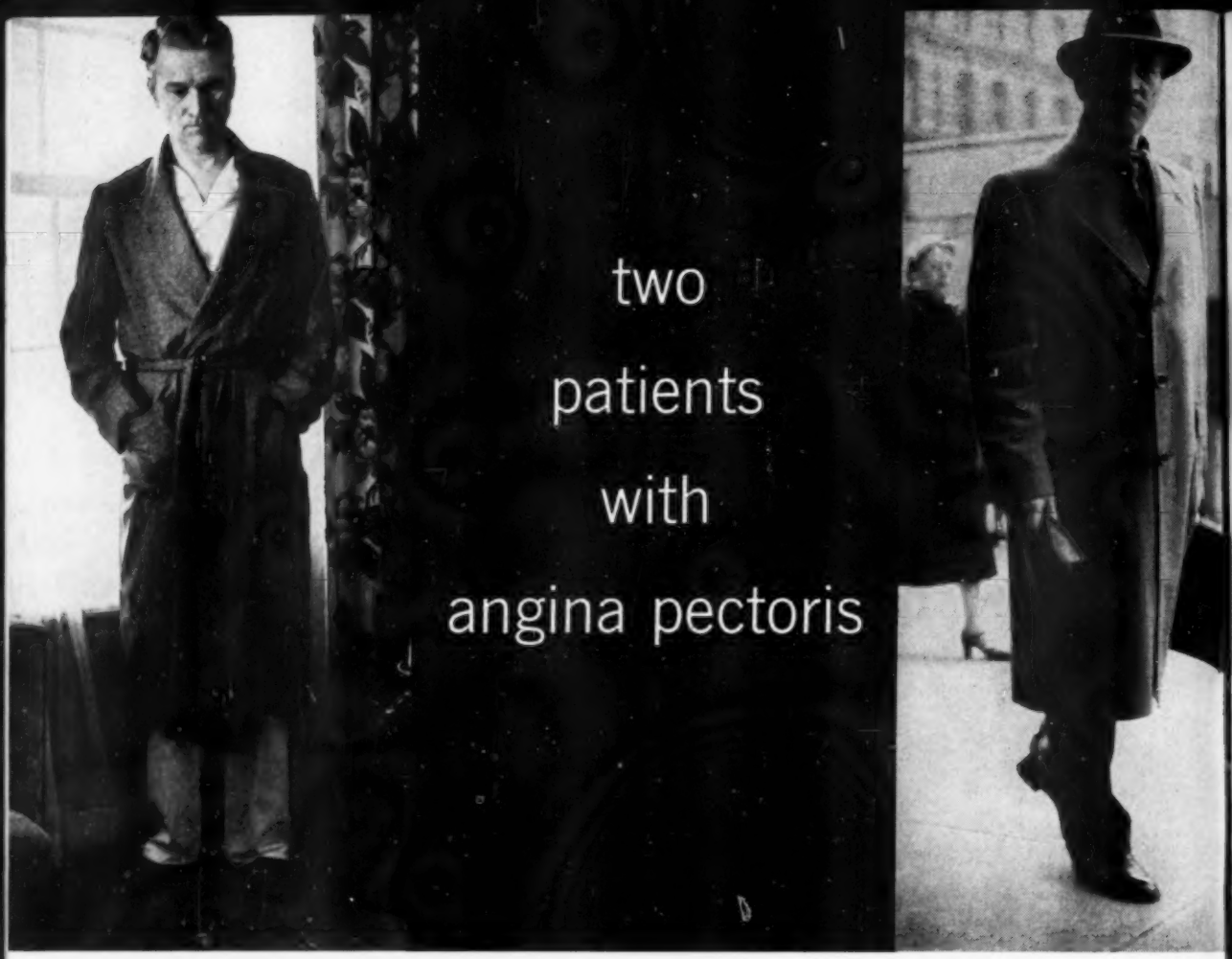

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References: **1.** Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. *230*:254 (Sept.) 1955. **2.** Kory, R. C., *et al.*: Am. Heart J. *50*:308 (Aug.) 1955. **3.** Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1953. **4.** Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. **5.** Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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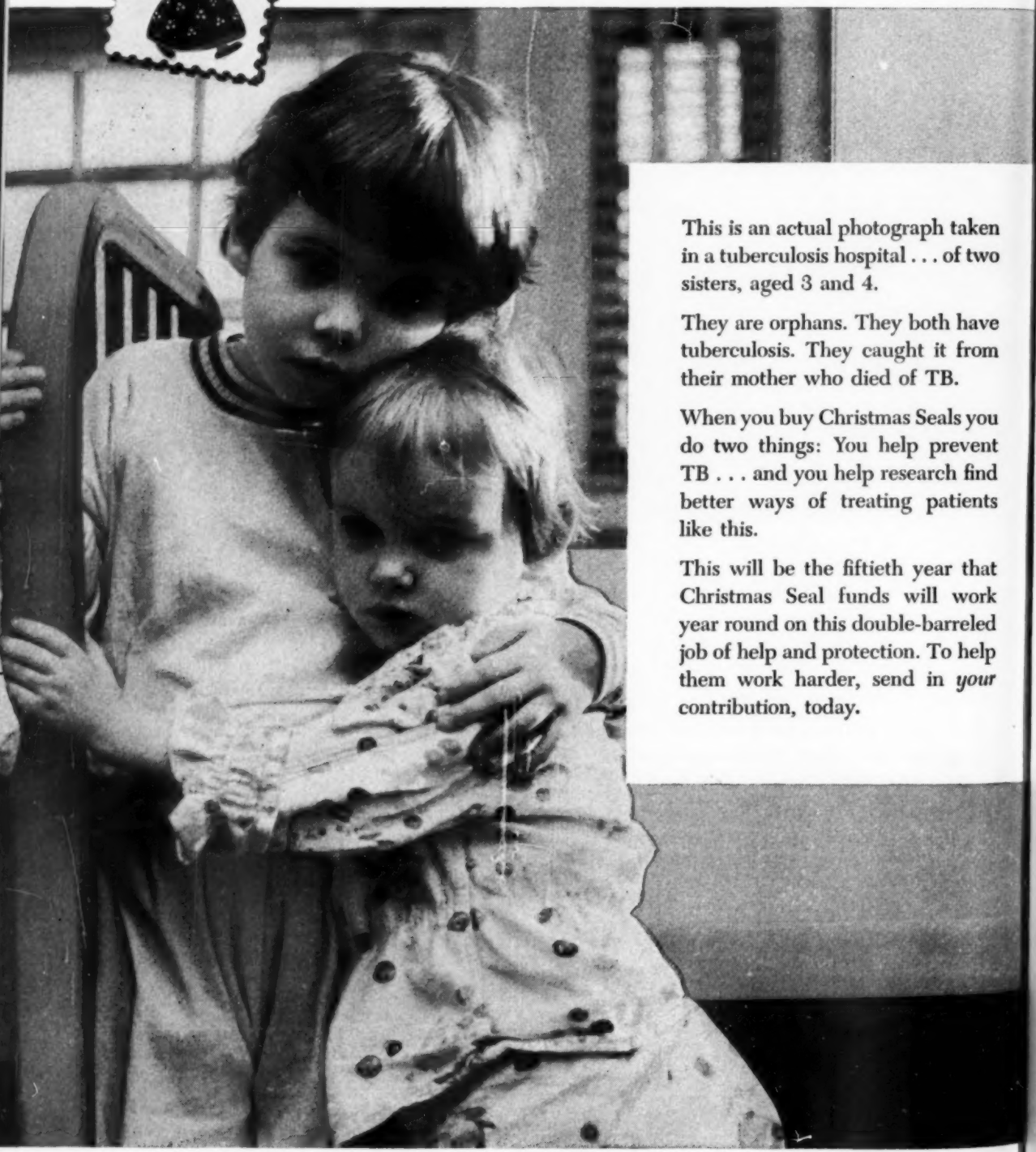

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D.
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* * *

E.
Summary of QRS-T Patterns in Unipolar Thoracic and Limb Leads.

This work is the outgrowth of previous manuals prepared to supplement the Graduate Course in Electrocardiography given at Wayne University College of Medicine for many years. The objective is an organized presentation of the interpretation of the unipolar electrocardiogram. The only basic physics included is that considered essential to the interpretation of the tracing; controversial theories that do not contribute to clinical analysis have been omitted.

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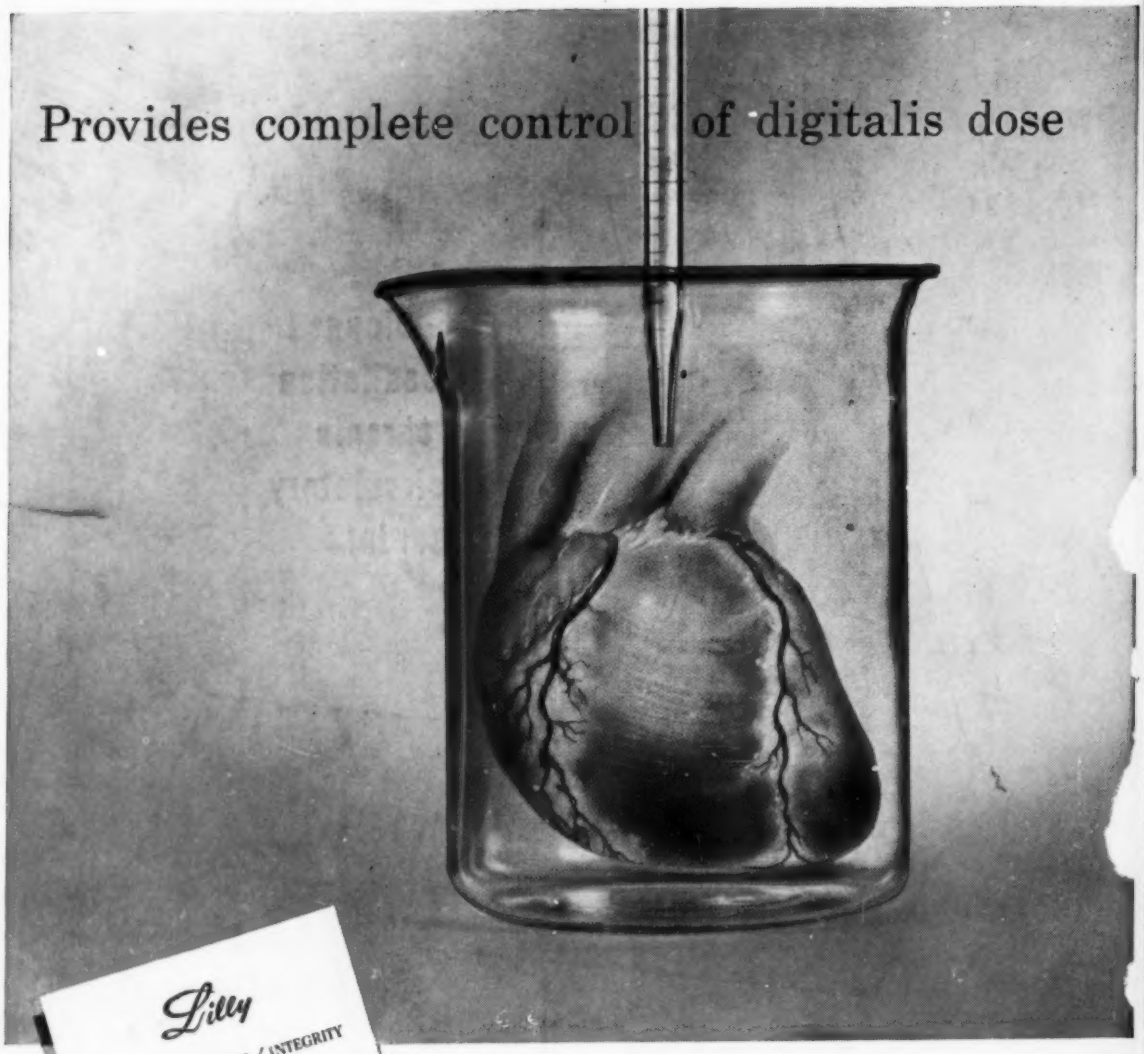
RONIACOL 'ROCHE'

acts primarily on the small arteries and arterioles to enhance collateral circulation.

Especially useful for long-term therapy in older patients whose feet are "always cold."

RONIACOL® BRAND OF BETA-PYRIDYL CARBINOL



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'Crystodigin'

(CRYSTALLINE DIGITOXIN, LILLY)

. . . . . permits accurate dosage titration to produce the maximum therapeutic effect

Since initial digitalization and maintenance dosage must be carefully individualized, 'Crystodigin' fulfills the important requirements of a preferred digitalis. 'Crystodigin' is a crystalline-pure, uniformly potent single glycoside that is completely absorbed in the gastro-intestinal tract. With 'Crystodigin,' the maximum therapeutic effect can be safely determined by dosage titration in increments as small as 0.025 mg.

Available in scored tablets of 0.05 mg. (orange), 0.1 mg. (pink), 0.15 mg. (yellow), and 0.2 mg. (white); and in 1-cc. and 10-cc. ampoules, 0.2 mg. per cc.

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